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ASSESSMENT INTEGRATO NELLA DIPENDENZA DAL GIOCO D'AZZARDO: DALLA PSICODIAGNOSI AL NEUROIMAGING

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Exechias, anfora campaniforme a figure nere, Musei Vaticani, Città del Vaticano

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GENERAL INTRODUCTION

Most people gamble on a social basis spending a limited amount of time in gamble related activities with predetermined acceptable losses. However, despite social gambling is practiced in every age, culture and different social conditions, it is now clear that for vulnerable people it can be a risk of incurring in a disease defined as Pathological Gambling (PG). PG is characterized by an inability to adopt a control on gambling and on losses and a considerable need to gamble. Previous studies highligthed that every game has a potential to produce a gambling disorder (La Barbera and La Cascia 2008). PG was added to the DSM in 1980 (APA 1980), largely due to the efforts of Dr. Robert Custer, who had treated pathological gamblers and written about their illness for several years. This disorder was classified as a "*Disorder of Impulse Control*", because one of the most behavioural trait associated to this disorder is the impulsivity and the impulse dyscontrol (Marazziti et al., 2014; Picone 2010).

During the last twenty years, a substantial body of research has highlighted many similarities between PG and drug dependence (Petry et al. 2013; Potenza 2014). It was shown the presence of common psychopatological symptoms between the two disorders (Petry 2006; Toce-Gerstein et al. 2003), similar comorbidities (Kessler et al. 2008; Lorains et al. 2011; Nalpas et al. 2011; Petry et al. 2005), common genetics vulnerability (Black et al. 2006; Blanco et al. 2012; Slutske et al. 2000), similar biological markers and cognitive deficits (Potenza et al. 2003; Reuter et al. 2005). Furthermore, the same neuroanatomical and neurochemical features underlie the occurrence of the common behavioural phenotype, i.e. tolerance, withdrawal and craving (Goudriaan et al. 2004; Leeman & Potenza 2012; Potenza 2013). Moreover, pathological gambling behavior is characterized by a continuous pursuit of money to gamble or for paying debts connected to the gamble. This mechanism is called "*chasing of losses*" and brings these patients to an escalation of the frequency of gamble (Gainsbury et al. 2014). These dysfunctional behaviours, similarly to the drug addicted, can lead to a vicious circle that promotes a worsening of economic and affective states in gamblers.

Taking this into consideration, the new edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) categorizes pathological gambling as a "*Behavioural addictive disorder*" (American Psychiatric Association, 2013).

DSM-5 Diagnostic Criteria to make diagnosis of Gambling Disorder:

A. Persistent and recurrent problematic gambling behavior leading to clinically significant impairment or distress, as indicated by the individual exhibiting four (or more) of the following in a 12-month period:

1 Needs to gamble with increasing amounts of money in order to achieve the desired excitement.

2 Is restless or irritable when attempting to cut down or stop gambling.

3 Has made repeated unsuccessful efforts to control, cut back, or stop gambling.

4 Is often preoccupied with gambling (e.g., having persistent thoughts of reliving past gambling experiences, handicapping or planning the next venture, thinking of ways to get money with which to gamble).

5 Often gambles when feeling distressed (e.g., helpless, guilty, anxious, depressed).

6 After losing money gambling, often returns another day to get even ("chasing" one's losses).

7 Lies to conceal the extent of involvement with gambling.

8 Has jeopardized or lost a significant relationship, job, or educational or career opportunity because of gambling.

9 Relies on others to provide money to relieve desperate financial situations caused by gambling.

B. The gambling behavior is not explained by a manic episode.

Specify if*:*

- **Episodic:** Meeting diagnostic criteria at more than one time point, with symptoms subsiding between periods of gambling disorder for at least several months.
- **Persistent:** Experiencing continuous symptoms, to meet diagnostic criteria for multiple

years.

Specify if*:*

- **In early remission:** After full criteria for gambling disorder were previously met, none of the criteria for gambling disorder has been met for at least 3 months but for less than 12 months.
- **In-sustained remission:** After full criteria for gambling disorder were previously met, none of the criteria for gambling disorder has been met during a period of 12 months or longer.

Specify current severity:

- **Mild:** 4–5 criteria met.
- **Moderate:** 6–7 criteria met.
- **Severe:** 8–9 criteria met.

In Italy, PG prevalence ranges approximately from 0.5 -2.2 %, thus representing both social and health costs in terms of pharmacological and psychological therapies (Cowlishaw et al. 2012; Lejoyeux 2012; Serpelloni 2013). Furthermore, PG is often associated to comorbidity with other psychopathological disorders. Indeed comorbid Axis I psychiatric conditions, such as major depression, anxiety, obsessive-compulsive and panic disorders, substance abuse, Axis II personality disorders are commonly diagnosed in gambling addicted (Giddens et al. 2012; Kerber et al. 2008; Odlaug et al. 2012; Ortiz-Tallo et al. 2011; Shek et al. 2012). The presence of comorbidity disorders makes more complicated treating effectively these patients (Yip and Potenza 2014). Moreover, several markers of psychopathology such as risk-taking, impulsivity, sensation seeking and emotional dyscontrol, contribute to the onset and to the worsening of PG (Kraplin et al. 2014; Spurrier & Blaszczynski 2014; Steel & Blaszczynski 1998) as well as peer group influence (Langhinrichsen-Rohling 2004) and environmental factors such as a large availability of gamble machines in the territory (Ladouceur 1999).

A further step in the investigation of pathological gambling consisted in incorporating neuropsychological and neuroimaging approaches. They indicate differences between pathological gamblers and healthy controls regarding the activation of several brain circuits during cognitive control (Potenza et al. 2003) and abnormal activation of the brain's reward circuitry during winning and/or losing money (Reuter et al. 2005; van Holst. 2012). Furthermore, other studies highlighted an over-activation of the motivational system during the presentation of gambling cues (Crockford et al. 2005).

The Italian Department for Anti-Drug Policies (DPA) provided a complex definition of PG: "*pathological gambling is a behavioural addiction with health and social consequences that require diagnosis, treatment and rehabilitation. This disease is often chronic and characterized by the presence of craving and risk of relapse*". " (Serpelloni 2013).

This definition highlights the importance of considering PG as a neuro-psycho-biological disorder influenced by social factors, requiring a complex assessment process and evidence-based therapies. Both diagnosis and treatment of pathological gamblers need to swing from a *nomothetic* approach, important for obtaining objective knowledge on PG through scientific methods and an *idiografic* approach, focuses on the specific peculiarity of the treatment-seeking subjects. Research activity is relevant for understanding the specific psychological, social, neurobiological and neurofunctional alterations related to PG and these body ok knowledge has direct repercussion on the treatment strategies. In this regard research on PG and clinical activity are related by relationship of interdependence assuming the same importance.

This is congruent with my thesis vision. The research is focused on a multidimensional assessment of pathological gamblers, taking into consideration the possible clinical repercussion. This research is orginized in four different but intercorrelated parts.

The **first part** of this thesis evaluates the presence of Axis I and Axis II comorbidities in 70 pathological gamblers, compared to 70 healthy controls, through a psychodiagnostic approach.

The **second part** investigates the relevant role of alexithymia and anger expression in PG. One hundred treatment-seeking pathological gamblers, compared to 100 HCs, were evaluated using psychological assessment.

The **third part** orients the assessment process through the neurohormonal and neurovegetative point of view. We investigate the effect of the Trier Social Stress Test on cortisol and on interbeat interval in relation to impulsivity measure in a sample of male pathological gamblers, compared to healthy controls.

Finally the **fourth part** of the thesis uses a neurofunctional approach to investigates the salience attribution and the inhibitory control in pathological gamblers tested in a Go-NoGo task during a functional magnetic resonance sesssion

All of these points of view on PG, psychological, neurohormonal, neurovegetative and neurofunctional appear all useful and complementary to understand the clinical characteristics of pathological gamblers and could be relevant to improve evidence-based therapies.

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PART 1

PSYCHODIAGNOSTIC ASSESSMENT OF PATHOLOGICAL GAMBLERS: A FOCUS ON PERSONALITY DISORDERS, CLINICAL SYNDROMES AND ALEXITHYMIA

1.1 INTRODUCTION

In the first part of my thesis, a study concerning the presence of Axis I and Axis II comorbidity in pathological gambling is presented through an investigation by a psychodiagnostic approach.

1.2 BACKGROUND

Large evidence suggests that pathological gamblers (PGs) exhibit specific personality traits, such as risk-taking, impulsivity and sensation seeking (Odlaug et al., 2013; Sharpe, 2002; Spurrier & Blaszczynski, 2013; Steel & Blaszczynski, 1996). Personality traits implicated in the etiology of pathological gambling, significantly overlap with those identified for borderline personality disorder and substance use disorders (Kotov et al., 2010; Samuel & Widiger, 2008). Furthermore, a large percentage of PGs display co-occurring clinical syndromes such as major depression, anxiety, obsessive compulsive, panic and substance abuse disorders, and various personality disorders (Kerber et al., 2008; Lorains et al., 2011; Odlaug et al., 2012; Shek et al., 2012). Psychiatric comorbidity is considered a major risk factor for pathological gambling, and the co-occurrence of a personality disorder and specific personality traits may affect the clinical presentation and treatment outcomes (Odlaug et al., 2013). Indeed, a linear association between gambling disorder severity and comorbid Axis I-disorders have been reported (Bischof et al, 2013). As far as we know, very few studies use the Millon Clinical Multiaxial Inventory (MCMI-III) for assessing co-occurring personality disorders and clinical syndromes in PGs. They show that pathological gambling is associated with avoidant and compulsive personality patterns, as well as with self-defeating and dysthymic disorders (Henderson, 2004). On the other hand, Ortiz-Tallo et al (2011) identified four

clinical personality patterns in PGs: dependent-, obsessive-compulsive-, narcissistic- and antisocial-phenotype, that are differently associated with clinical syndromes.

It is worth noting that patients suffering from different personality disorders and clinical syndromes have high levels of alexithymia (De Rick & Vanheule, 2007; Leweke et al., 2012; Nicolò et al., 2011). Alexithymia refers to the difficulty in identifying and describing feelings, the tendency to minimize emotional experiences and the inclination to an externally oriented way of thinking (Taylor, 1997). Several studies report high alexithymia scores in addictive disorders (Dorard et al., 2008; El Rasheed, 2001; Scimeca et al, 2014; Taylor et al., 1997; Thorberg et al., 2009; van Rossum al., 2004), including pathological gambling (Parker et al., 2005). Interestingly, different levels of alexithymia may be detected in different subtypes of PGs: indeed racetrack, slot-machine, cards and lotteries gamblers, differ in their alexithymia scores (Bonnaire et al., 2009; 2013; Toneatto et al., 2009). Multiple determinants are interrelated and operate across individual and environmental levels in setting up the multifaceted framework of gambling behaviour. Thus, a multilevel approach could help in the interpretation of different features of pathological gambling, and in the analysis of how personality disorders, clinical syndromes and dysfunctional emotional regulation operate, separately and in combination, on the determination of gambling behaviour. Importantly, the assessment of a relationship between alexithymia and gambling behaviour, over and above the influence of Axis I and Axis II psychiatric disorders, could have clinical and therapeutic relevance both in orienting diagnostic assessment and developing proper treatments. Moreover, since alexithymia is associated with negative treatment outcomes (Cleland et al., 2005; Loas et al., 1997; Ogrodniczuk et al., 2004, 2005; Ziolkowski et al., 1995), a more accurate analysis of the processes that regulate and control emotional behaviour could play a role in the definition of the best practices for a successful management of PGs.

Given these premises, the first aim of the present study is to assess co-occurring personality disorders and clinical syndromes, together with alexithymia levels, in PGs; the second aim is to verify whether alexithymia could affect the association between psychopathological disorders and

gambling behaviour. Particularly, we are interested in determining whether a relationship between gambling behaviour and alexithymia exists, after controlling for Axis I and Axis II disorders.

1.3 PARTICIPANTS AND PROCEDURE

A total of 70 consecutive treatment-seeking PGs, recruited at the *"Center for dependence without drugs"* (CeDiSS) in Palermo, and 70 healthy controls (HC), recruited by advertisements, were included in the study. Both groups consisted of people ranging from 18-60 years. Groups were matched for age, sex and years of education. In the HC group the inclusion criteria were the absence of past or present conditions of pathological gambling behaviour. Furthermore, in both groups, subjects with a history of serious neurological disorders and past or present drug abuse or drug addiction, were excluded. The study was introduced to the participants as an investigation concerning personality traits, emotional expression and gambling behaviour, and they were asked to answer anonymously self-report questionnaires. All measures were administered under respect of privacy. A signed informed consent was obtained from each subject after the procedures were fully explained.

1.4 MEASURES

1.4.1 Socio-demographic Variables

A socio-demographic questionnaire was used to ask participants about their age, sex, marital status, occupation, habitual residence, and socioeconomic status.

1.4.2 Gambling Behaviour Assessment

All subjects completed the South Oaks Gambling Screen (SOGS). The SOGS is a 20-item questionnaire that measures gambling behaviour through questions on participant's history of gambling, the frequency of these behaviours, and obstacles that gambling may have posed in the participant's life. The total score on the SOGS ranges from 0 to 20 (scores higher than 4 indicate

probable pathological gambling) (Lesieur, & Blume, 1987).

1.4.3 Personality disorders and clinical syndromes

To evaluate personality disorders and clinical syndromes we used the third version of Millon Clinical Multiaxial Inventory (MCMI-III) (Millon, 1994). MCMI-III is a 175-item true/false self-report instrument that assesses Axis I and Axis II psychopathology. Based on Theodore Millon Evolutionary Theory of personality and psychopathology, the MCMI-III identifies 14 personality disorder scales and 10 clinical syndrome scales. The MCMI-III raw scores are reported as weighted base rate (BR) scores. Previous studies have shown good internal consistency (α = .66–.90) and stability (test-retest r = .84–.96) for the MCMI-III scales (Zennaro, Ferracuti, Lang & Sanavio, 2008).

1.4.4 Alexithymia

Alexithymia was measured with the Italian version of the Toronto Alexithymia Scale (TAS-20) (Bagby, Parker, & Taylor, 1994). The TAS-20 is a 20-item self-report inventory measuring alexithymia as a three-dimensional construct of Difficulty Identifying Feelings (DIF), Difficulty Describing Feelings (DDF), and Externally Oriented Thinking (EOT). Participants were asked to respond to these items on a five-point likert-scale of "greatly disagree", "disagree", "no comment", "agree", and "greatly agree", scoring from 1 to 5. Individuals were assessed with pathological levels of alexithymia if their score was 61 or above. Previous studies have shown that the Italian version of the TAS-20 has good internal consistency (Cronbach's alpha of .75 and .82 in normal and clinical groups, respectively) and test–retest reliability over a 3-week interval (r = .77) (Bressi et al, 1996).

1.5 STATISTICAL ANALYSIS

A Chi-Squared Test was used to evaluate significant differences between PGs and non-PGs on the MCMI-III scores. Univariate analysis of the variance (ANOVA) was used to compare alexithymia levels in the two groups. Hierarchical Multiple Regression was used to evaluate whether there was a relationship between pathological gambling behaviour and alexithymia scores,

after controlling for personality disorders and clinical syndromes. Statistical analysis was performed on SPSS for Windows 17.0.

1.6 RESULTS

Data analysis from demographic information revealed no significant differences between groups on socio-demographic variables, such as sex, age and education level (Table 1). In terms of favorite gambling patterns, in PGs group, the most prevalent categories included sport betting (76%), slot machines (58%), scratch card (55%), lottery (34%), card games (27%), and bingo (26%). The percentage of PGs who received one or more diagnosis of personality disorders were 51.42%, while the other 48.58% did not receive any personality disorder diagnosis. A noteworthy 26.8% of PGs was scored for two or more personality disorders. Table 2 shows the significant differences in the assessment of personality disorders, clinical syndromes and alexithymia levels in PGs and non-PGs in several scales of MCMI-III. In particular, as far as Axis I syndromes concern, PGs showed higher Anxiety ($\chi^2 = 16.565$, $p < .001$), Somatoform symptoms ($\chi^2 = 7.368$, $p < .01$), Bipolar Manic Symptoms ($\chi^2 = 6.269$, $p < .05$), Dysthymia ($\chi^2 = 12.495$, $p < .001$) and Major Depression ($\chi^2 = 3.877 < .05$). PGs scoring were significantly higher in several Axis II personality disorders such as Depressive ($\chi^2 = 20.236$, $p < .001$), Antisocial ($\chi^2 = 11.938$, $p < .001$), Sadistic ($\chi^2 = 7.368$, $p < .01$), Passive-Aggressive (Negativistic) ($\chi^2 = 13.831$, $p < .001$), Self-Defeating ($\chi^2 = 8.485$, $p < .005$), Borderline ($\chi^2 = 4.155$, $p < .05$) and Paranoid ($\chi^2 = 5.185$, $p < .05$). When alexithymia levels were explored (Table 3), significantly higher scores were observed in PGs, compared to non-PGs on the total score of the TAS-20 ($F (1,138) = 13,656$, $p < .001$), on the second subscale (Difficulty Describing Feelings), ($F (1,138) = 8,470$, $p < .005$) and on the third subscale (Externally-Oriented Thinking), ($F (1,138) = 16,741$, $p < .001$).

To verify our second hypothesis, we performed a hierarchical multiple regression analysis on all subjects, in which personality disorders and clinical syndromes were added on the first step (Model 1), and alexithymia was added on the second step (Model 2). Multicollinearity was assessed

using the variance inflation factor (VIF). VIF scores ranged between 1.238 and 3.106 and the larged condition index was less than 10, suggesting a lack of significant multicollinearity (Belsley, 1991). According to our hypothesis, personality disorders and clinical syndromes were significant predictors of SOGS scores (Table 4), accounting for 65% of the variance (Model 1); it is worth considering that adding alexithymia scores in the second step significantly increased by 5.2% the explained variance in SOGS scores, contributing to a great extent to the prediction of gambling behaviour (Model 2).

Table 1: *Statistics of the sample by gender, age and years of education*

FACTOR	PATHOLOGICAL GAMBLERS (n=70) Frequency (%)	HEALTHY CONTROL GROUP (n=70) Frequency (%)	χ^2
SEX Male	60 (83.3)	58 (80.0)	.21 NS
	PATHOLOGICAL GAMBLERS (n=70) Mean (St. Dev.)	HEALTHY CONTROL GROUP (n=70) Mean (St. Dev.)	F
MEAN AGE (years)	42.41 (10.506)	41.28 (13.55)	.303 NS
MEAN EDUCATION (years)	11.21 (2.69)	12.07 (2.59)	3.67 NS

Note. NS Non significant; *p < .05; **p < .01; ***p < .005; ****p < .001.

Table 2: *Statistics of MCMI-III scores between groups*

FACTOR	TOTAL (n=140) Frequency (%)	PATHOLOGICAL GAMBLERS (n=70) Frequency (%)	HEALTHY CONTROL GROUP (n=70) Frequency (%)	χ^2	Phi
MCMI-III *CLINICAL SYNDROMES SCALES*					
Anxiety	27 (19.28)	23 (32.85)	4 (5.71)	16.56 ****	.34
Somatoform	7 (5.0)	7 (10.0)	-	7.36 **	.22
Bipolar: Manic	6 (4.28)	6 (8.57)	-	6.26 *	.21
Dysthymia	18 (12.85)	16 (22.85)	2 (2.85)	12.49 ****	.29
Alcohol Dependence	-	-	-	-	-
Drug Dependence	2 (1.42)	2 (2.85)	-	2.02 NS	-
Post-Traumatic Stress Disorder	3 (2.14)	3 (3.06)	-	3.06 NS	.14
Thought Disorder	4 (2.85)	4 (5.71)	-	4.11 NS	.17
Major Depression	10 (7.14)	8 (11.42)	2 (2.85)	3.87 *	.16
Delusional Disorder	6 (4.28)	3 (4.28)	3 (4.28)	.00 NS	.00
PERSONALITY DISORDERS SCALES					
Schizoid	9 (6.42)	7 (10.0)	2 (2.85)	2.96 NS	.14

Avoidant	10 (7.0)	6 (8.57)	4 (5.71)	.43 NS	.05
Depressive	27 (19.28)	24 (34.28)	3 (4.28)	20.23 ****	.38
Dependent	25 (17.85)	14 (20.0)	11 (15.71)	.43 NS	.05
Histrionic	3 (2.14)	-	3 (4.28)	3.06 NS	.14
Narcissistic	22 (15.71)	10 (14.28)	12 (17.14)	.21 NS	.03
Antisocial	11 (7.85)	11 (15.71)	-	11.93 ****	.29
Aggressive (Sadistic)	7 (5.0)	7 (10.0)	-	7.36 **	.22
Compulsive	-	-	-	-	-
Passive-Aggressive (Negativistic)	16 (11.42)	15 (21.42)	1 (1.42)	13.83 ****	.31
Self-Defeating	8 (5.71)	8 (11.42)	-	8.48 ***	.24
Schizotypal	3 (2.14)	3 (4.28)	-	3.06 NS	.14
Borderline	13 (9.28)	10 (14.28)	3 (4.28)	4.15 *	.17
Paranoid	5 (3.57)	5 (7.14)	-	5.18*	.19

Note. NS Non significant; *p < .05; **p < .01; ***p < .005; ****p < .001.

Table 3: *Statistics of alexithymia levels between groups*

FACTOR	TOTAL (n=140) M (SD)	PATHOLOGICAL GAMBLERS (n=70) M (SD)	HEALTHY CONTROL GROUP (n=70) M (SD)	F	PARTIAL ETA-SQUARED
TAS-20 Total Score	46,52 (12,92)	50,38 (13,408)	42,65 (11,24)	13.65 ****	.93
Difficulty Identifying Feelings (DIF)	40,62 (17,68)	42,68 (19,47)	38,57 (15,55)	1.908 NS	.84
Difficulty Describing Feelings (DDF)	52,75 (20,19)	57,59 (20,57)	47,91 (18,72)	8.47 ***	.87
Externally Oriented Thinking (EOT)	47,66 (14,35)	52,36 (14,96)	42,95 (12,08)	16.74****	.92

*Note. NS Non significant; *p < .05; **p < .01; ***p < .005; ****p < .001.*

Table 4. *Hierarchical multiple regression analysis predicting pathological gambling behaviour*

FACTOR	Model 1					Model2				
	β	*t*	*p*	*r*	*sr*	*β*	*t*	*p*	*r*	*sr*
Anxiety	-,128	-,945	,347	,439	-,053	-,115	-,894	,373	,439	-,047
Somatoform	-,062	-,431	,667	,476	-,024	,063	,450	,654	,476	-,024
Bipolar: Manic	,136	1,427	,156	,400	,079	,177	1,942	,055	,400	,102
Dysthymia	,246	1,478	,142	,573	,082	,121	-,752	,454	,573	,039
Alcohol Dependence	-,272	-2,147	,034	,406	-,119	-,269	-2,228	,028	,406	-,117
Drug Dependence	-,138	-,989	,325	,353	-,055	-,131	-,979	,330	,353	-,051
Post-Traumatic Stress Disorder	,223	1,551	,124	,579	,086	,317	2,308	,023	,579	,121
Thought Disorder	-,116	-,808	,421	,473	-,045	-,142	-1,039	,301	,473	-,054
Major Depression	,128	,758	,450	,492	,042	,038	,236	,814	,492	,012
Delusional Disorder	-,113	1,122	,264	,499	,062	,117	1,211	,228	,499	,063
Schizoid	-,230	-2,024	,045	,429	-,113	-,310	-2,815	,006	,429	-,147

Avoidant	-,301	-2,476	,015	,216	-,138	-,387	-3,129	,002	,216	-,164
Depressive	-,044	,356	,723	,492	,020	,002	,018	,986	,492	,001
Dependent	,275	2,048	,043	,425	,114	,246	1,910	,059	,425	,100
Histrionic	-,334	-2,969	,004	-,275	-,165	-,369	-3,426	,001	-,275	-,179
Narcissistic	,292	2,729	,007	,139	,152	,225	2,116	,037	,139	,111
Antisocial	,425	2,240	,027	,483	,125	,443	2,460	,015	,483	,129
Aggressive (Sadistic)	-,017	-,155	,877	,371	-,009	,024	,224	,823	,371	,012
Compulsive	-,283	-2,942	,004	-,542	-,164	-,183	-1,875	,063	-,542	-,098
Passive-Aggressive (Negativistic)	-,129	-,867	,388	,443	-,048	-,042	-,297	,767	,443	-,016
Self-Defeating	,117	,795	,428	,405	,044	,192	1,359	,177	,405	,071
Schizotypal	-,113	-1,132	,260	,339	-,063	-,105	-1,110	,269	,339	-,058
Borderline	,232	1,323	,189	,562	,074	,228	1,367	,174	,562	,072
Paranoid	-,001	,008	,994	,440	-,000	-,078	-,628	,531	,440	-,033
TAS-20 Total Score						3,738	1,937	,055	,430	,101
Difficulty Identifying Feelings (DIF)						-1,814	-1,959	,053	,286	-,102
Difficulty Describing Feelings (DDF)						-1,612	-2,092	,039	,312	-,109
Externally Oriented Thinking (EOT)						-1,417	-1,655	,101	,378	-,087
Model R^2	,650					,702				
R^2 Change	,570					,620				
F	(26,113) =	8,073****				(4,109)=	4,725***			

*Note. NS Non significant; *p < .05; **p < .01; ***p < .005; ****p < .001.*

1.7 DISCUSSION

The aim of this research was to investigate the relationship between personality disorders, clinical syndromes and emotional regulation in a group of treatment-seeking PGs, compared with a healthy control group. Moreover, we focus our attention on the relevance of alexithymia construct as a predictor of gambling behaviour, after controlling for the role of personality disorders and clinical syndromes. In agreement with research which indicates high prevalence of comorbid psychopathological conditions in PGs, we highlighted, as expected, higher rates of comorbid clinical syndromes and personality disorders in treatment-seeking PGs, with respect to controls. According to the Pearson's chi-squared test, PGs displayed significantly higher scores for Axis I disorders, such as anxiety, somatoform symptoms, bipolar disease, dysthymia and major depression,

with respect to controls; moreover, they showed increased levels of Axis II personality disorders like depressive, antisocial, sadistic, negativistic, self-defeating, borderline and paranoid disorders.

Among treatment-seeking PGs, we observed a significant prevalence of antisocial and borderline personality disorders, in agreement with recent estimates (Dowling et al., 2014). Nevertheless, among our experimental group of treatment-seeking PGs, depressive, passive-aggressive and dependent disorders were the most prevalent. Several studies indicate that pathological gambling is highly comorbid with substance abuse, mood disorders, anxiety and personality disorders such as antisocial, borderline, histrionic and narcissistic disorders (Bagby et al., 2008; Petry et al., 2005; Sacco et al., 2008).

Other studies identify a relationship between Cluster A and C diagnosis and pathological gambling in treatment samples (Specker et al., 1996; Steel & Blaszczynski, 1998). Moreover, variability between distinct typologies of PGs exists, with higher rates of cluster B personality disorders in offline gamblers and higher rates of cluster C personality disorders in online gamblers (Barrault & Varescon, 2012). As a matter of fact, evidence on the specific comorbidities occurring in pathological gambling is poorly consistent. As a consequence, in this study a complete diagnostic tool such as MCMI-III was employed, in order to evaluate specific personality disorders that are not included in the new edition of the Diagnostic and Statistics Manual of Mental Disorders (DSM-5), and provide a broader clinical evaluation. With regard to this, the relevant presence of dependent and narcissistic disorders, among others, could be related to different subtypes of PGs. Indeed, pathological gambling has been conceptualized as a heterogeneous diagnostic category, characterized by various psychopathological traits that can amount to different typologies of PGs (Blaszczynski & Nower, 2002).

An important outcome of the present study concerns the relevant alexithymia levels in treatment-seeking PGs; indeed, PGs displayed higher alexithymia total score, more difficulty in describing feelings to other people and increased externally-oriented thinking, with respect to controls. Deficits in emotional processing are central to the notion of alexithymia, in that

alexithymic individuals attempt to regulate their emotions through compulsive and impulsive behaviour, due to their inability to modulate emotions through cognitive processing (Taylor et al., 1997). Hence, individuals with alexithymia may be prone to develop pathological gambling, as confirmed by several prevalence studies (Mitrovic & Brown, 2009; Parker et al., 2005), and further strengthened by our results. Taking advantage of the diagnostical instruments used in this study, which include the assessment of a broader spectrum of personality disorders, clinical syndromes and dysfunctional emotional regulation in gambling addiction, our results contribute to characterizing comorbidity in PGs, with the purpose of producing the best diagnosis and designing specific and tailored treatments.

A further relevant outcome of this study consists in the relationship between gambling behaviour and alexithymia, after controlling for Axis I and Axis II disorders. Pathological gambling behaviour is a multidimensional clinical phenomenon, associated with several emotional and social factors. Thus, comorbid psychopathological conditions and alexithymia levels were analyzed as predictors of gambling behaviour, by using hierarchical multiple regression analysis. Our results indicate that alexithymia affects gambling behaviour over and above comorbid personality disorders and clinical syndromes. Although the relationship between alexithymia and Axis I and Axis II disorders is well-known, we did find that alexithymia was associated to gambling behaviour independently, constituting a further predictive factor. This latter finding underlines the importance of the assessment of alexithymia as a necessary step in the clinical evaluation of PGs, together with Axis I and Axis II disorders. Alexithymia, and in particular the difficulty in describing and regulating emotions, leads the individual to discharge emotions through impulsive behaviour, that may predispose to pathological gambling. Impulsive tendencies in PGs are associated with decreased ventral striatal activations in response to reward anticipation. As revealed by neuroimaging studies, PGs show reduced activity of the ventromedial prefrontal cortex, insula and ventral striatum during the Monetary Incentive Delay Task (MIDT), a test able to identify brain activation changes associated with reward/loss prospect, reward/loss anticipation and reward/loss

notification (Balodis et al, 2012; de Ruiter et al, 2009; Potenza, 2013). These findings show the neural and functional correlates of high levels of impulsivity in PGs, which might be correlated to high alexihtymia levels. On the other hand, observations on Parkinson's disease patients in treatment with D3 agonist show a significant prevalence of pathological gambling; indeed the stimulation of mesolimbic D3 receptors by these drugs is thought to underlie the development of impulsive behaviour (Vilas et al, 2012).

The present research has some limitations, especially concerning the recruitment of PGs, who were treatment-seeking and predominantly males. Probably this limitation is due to cultural facets but appears to be in line with Italian statistics, concerning treatment-seeking subjects for gambling problems (Serpelloni, 2013). Furthermore, recent studies show that pathological gambling behaviour has a gender-specific course, with stronger statistical associations between gambling problems and major depression, dysthymia, panic disorder, and dependence in women than in men (Grant et al., 2012; Desai and Potenza, 2008). In this regard, a forthcoming clinical focus is needed on gender differences in gambling behaviour and co-occurring comorbidities. Another limitation of the study concerns the high number of predictors in comparison with the sample size (Harris R.J., 1985). This limitation appears to be related to the particular psychological tools utilized and to the difficulty in recruiting large sample of subjects in a monocentric clinical study.

On the other hand, the strength of this study consists in the use of a clinical test such as MCMI-III with a strong theoretical base, that allows the assessment of a broad spectrum of Axis I and Axis II disorders, even those not included in the official nomenclature but relevant to PGs subtyping; moreover, we were able to enrol an homogeneous group of PGs, at the same stage of psychotherapy, and to compare them with a proper control group, matched for age, gender and education.

In conclusion, this study shows that patients suffering from pathological gambling display high rates of co-occurring global psychopathology and in particular personality disorders, Axis I syndromes and dysfunctional modality of emotion regulation. The alexithymia construct stands out

as an important and independent predictor of gambling behaviour, thus orienting the therapeutic strategy also towards the treatment of this clinical feature. Indeed, a straightforward clinical implication of these findings may lie in the refinement of the diagnostic assessment of pathological gambling, as well as in the empowering of the prevention strategies.

Beyond diagnosis, however, the evaluation of alexithymia in PGs could affect the response to treatment. Indeed, alexithymia is associated with negative treatment outcomes, likely because of the setting up of an obstacle to the therapeutic alliance (Loas et al., 1997; Ziolkowski et al., 1995; Cleland et al., 2005; Ogrodniczuk et al., 2004, 2005). In this regard, as Parker et al. (2005) suggested, clinicians who develop treatment strategies that address gambling problems, may want to take into account the likelihood that many of their patients may have elevated levels of alexithymia. To project and realize a focused and evidence-based treatment of this disorder, clinicians should integrate specific psychotherapeutic techniques that improve identification and differentiation in emotionally dysfunctional patients. Accordingly it, could be of central importance to evaluate the effects of an integrated psychotherapeutic approach which takes into account also a body-centred work (Rispoli, 2004). Infact, an interesting possibility is that emotional processing tasks, may be used to train emotional skills among alexithymic PGs, such as recognition of emotional expressions in faces and recollection of emotional memories (Cook et al., 2013; Luminet et al., 2006). This could help coping with impulsive behaviour and provide a new tool able to affect the prognosis of pathological gambling.

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PART 2

ALTERATIONS IN THE EMOTIONAL REGULATION PROCESS IN GAMBLING ADDICTION: THE ROLE OF ANGER AND ALEXITHYMIA

2.1 INTRODUCTION

After showing a remarkable presence of comorbid psychiatric disorders in pathological gamblers, in this part we used a psychodiagnostic approach to investigate the role of alexithymia and anger expression in gambling disorder.

2.2 BACKGROUND

As far as we know, among the diverse underlying clinical constructs of pathological gambling that have already been investigated, anger expression has been mostly neglected so far (Bischof et al. 2013, Bonnaire et al. 2013; Odlaug et al. 2013) with the exception of few studies, which highlighted the frequent co-occurrence of anger and gambling (Aymamì et al. 2014; Goodyear-Smith et al. 2006; Korman et al. 2008). Anger is a primary emotional state that consists in feelings associated with the perception of being wronged by something or someone; it varies in intensity from mild irritation or annoyance to intense fury and rage. Anger as a trait is conceptually distinct from anger as a state, the former reflecting a general tendency to react angrily to situations, whereas the latter represents as a temporary feeling varying in intensity (Spielberger & Reheiser 2009). Anger is one of the emotional components of aggressive behaviour and when dysfuncionally espressed, it contributes to impulse dyscontrol as reported for binge eating disorder (Krug et al. 2008; Ramirez & Andreu 2006). Furthermore, it is wellknown that high anger symptoms increase relapse in substance use disorders and can consequently lead to dropout from treatments (Patterson et al. 2008). Therefore, given the analogies between drug addiction and pathological gambling, and taking into account that impulse dyscontrol is a central feature of the psychological setting of

pathological gamblers (PGs) (Marazziti et al. 2014), we have hypothesized that anger might play a relevant role in pathological gambling too. Traditionally anger is considered as a sex related variable (Fox et al. 2008): compared to men, women are reported to experience angry feelings more frequently, longer, and predominantly through a verbal modality (Fernández & Scott 2009). On the contrary, men tend to show more aggressive and violent behaviours towards objects or people (Campbell & Muncer 2008). The role of gender on anger expression in gambling behaviour has not been yet investigated. Furthermore, studies on PGs have focused their attention on the emotion regulation process, specifically on alexithymia as risk factor for the onset of pathological gambling (Parker et al. 2005). Addictive behaviours may even arise as an attempt of alexithymic subjects to try to self-regulate their emotions (Taylor et al. 1997). The relationship between alexithymia and anger has been evaluated by few studies providing evidence of a complex association between them. Compared to individuals in the low-alexithymia group, subjects in the high-alexithymia group exhibited more non-verbal anger (Berenbaum & Irvin 1996). Nevertheless it is unclear if anger could be predictive of a greater severity of gambling behaviour, independently from the relationship between alexithymia and gambling addiction. To answer this question we will use a multilevel approach that allows the assessment of the influence of different features of gambling disorders, in affecting gambling behaviour. More specifically, we will assess the unique and combined influence of alexithymia and anger expression on gambling behaviour.

Hence, this study was aimed at: i) assessing alexithymia levels and anger scores in PGs; ii) testing the correlation between alexithymia, anger and severity of gambling disorder; iii) verifying the occurrence of a relationship between gambling behaviour and anger, after controlling for alexithymia; iv) finding out whether gender plays a role on anger expression in pathological gambling.

2.3 PARTICIPANTS AND PROCEDURES

100 treatment-seeking PGs and consistent HCs, ranging 18-60 years, participated in the study. PGs were recruited from the "*Center for dependence without drugs*" (CeDiSS) in Palermo,

Italy, while HCs were recruited through advertisements. Groups were matched for age, sex and education. In the HCs the inclusion criteria were the absence of past or present conditions of pathological gambling behaviour. Exclusion criteria for both groups were: lifetime diagnosis of schizophrenia or other psychotic disorders; history of serious neurological disorders; past or present drug abuse or drug addiction; treatment for mental disorders other than pathological gambling in the past 12 mounths. The study was introduced to the participants as an investigation on emotional expression and gambling behaviour, and they were asked to answer self-report questionnaires anonymously. All measures were administered under respect of privacy. A signed informed consent was obtained from each subject after the procedures were fully explained.

2.4 MEASURES

2.4.1 Socio-Demographic Variables

A socio-demographic questionnaire was used to ask participants about their age, sex, marital status, occupation, habitual residence, and socio-economic status.

2.4.2 Gambling Behaviour Assessment

All subjects completed the South Oaks Gambling Screen (SOGS). The SOGS is a 20 items questionnaire that measures gambling behaviour through questions on participant's history of gambling, the frequency at which the person engages in these behaviours, and obstacles that gambling may have posed in the participant's life. The total score on the SOGS ranges from 0 to 20 (scores from 5 indicates probable pathological gambling) (Lesieur & Blume 1987).

2.4.3 Anger Expression

The STAXI–2 is a 57-item self-report measure of the intensity of anger experienced at a particular moment and the frequency with which the individual feels, expresses, and controls feelings of anger (Spielberger 1994). The “state anger” (S-Ang) scale comprises 15 items that measure the intensity of angry feelings and the extent to which a person feels like expressing anger

at a particular time. The S-Ang items are equally split into three subscales: “feeling anger” (S-Ang/F) “feeling like expressing anger verbally” (S-Ang/V) and “feeling like expressing anger physically” (S-Ang/P). The “trait anger” (T-Ang) scale consists of 10 items that measures one’s general propensity to experience anger. The T-Ang scale comprises two subscales: “angry temperament” (T-Ang/T) which measures the expression of anger without provocation and “angry reaction” (T-Ang/R), which measures the expression of anger in response to an external stimulus. The remaining 32 items provide scores on four scales: (i) “anger expression out” (AX-O), which consists of eight items that measure how often angry feelings are expressed in verbally or physically aggressive behavior; (ii) “anger expression in” (AX-I), which consists of eight items that measure how often angry feelings are experienced but not expressed and/or are suppressed; (iii) “anger control out” (AC-O), which consists of eight items that measure how often a person controls the outward expression of angry feelings; (iv) “anger control in” (AC-I), which consists of eight items that measure how often a person attempts to control angry feelings by calming down or cooling off. An “anger expression index” (AX Index) can also be computed as (AX-I + AX-O) − (AC-I + AC-O). The Italian STAXI–2 has shown adequate overlap with the original version (Pearson's correlations among scales of the original and Italian version in a sample of bilingual participants ranged from .68 to .93), internal consistency (Cronbach's αs of scales ranged from .67 to .93 in the normative sample), and robust factor structure (Comunian 2004).

2.4.4 Alexithymia

Alexithymia was measured with the Italian version of the Toronto Alexithymia Scale (TAS-20) (Bagby, Parker & Taylor 1994a; Bagby et al. 1994b). The TAS-20 is a 20-item self-report inventory measuring alexithymia as a three-dimensional construct of difficulty identifying feelings (DIF), difficulty describing feelings (DDF), and externally oriented thinking (EOT). The participants were asked to respond to these items on a five-point likert-scale of “greatly disagree”, “disagree”, “no comment”, “agree”, and “greatly agree”, scoring from 1 to 5. Individuals are

considered as showing pathological levels of alexithymia if their score is 61 or above. Previous studies have shown that the Italian version of the TAS-20 has good internal consistency (Cronbach's alpha of .75 and .82 in normal and clinical groups, respectively) and test–retest reliability over a 3-week interval (r = .77) (Bressi et al. 1996).

2.5 STATISTICAL ANALYSIS

Multivariate analysis of the variance (MANOVA) was used to evaluate significant differences between PGs and non-PGs on the TAS-20 and STAXI-2 scores. Bivariate Pearson's correlation was used to verify a correlation between alexithymia levels, anger levels and severity of gambling disorder. Hierarchical Multiple Regression was used to evaluate whether there was a relationship between pathological gambling behaviour and anger scores beyond the relationship between alexithymia and pathological gambling disorder. Additionally, a Hierarchical Multiple Regression was used to investigate the role of gender on anger expression in pathological gambling. All analysis were performed with an alpha of 0.05. Statistical analysis was conducted on SPSS for Windows 17.0.

2.6 RESULTS

Table 1 includes the descriptive data of both samples; no significant differences between groups on socio-demographic variables, such as sex, age and education level were found. Among the favorite gambling patterns, in the PGs group, the most prevalent categories included sports betting (64%), slot machines (54%), scratch card (58%), lottery (32%), card games (24%), and bingo (22%).

2.6.1 Alexithymia and anger scores

In order to ascertain the presence of higher state-anger and trait-anger in PGs, a multivariate analysis of variance (MANOVA) (using the Pillai's criterion) on STAXI-2 scores was used to evaluate differences between PGs and HCs that yielded a multivariate significance effect. Post-hoc

analysis indicated that, PGs reported significantly higher scores on all state-anger scales such as S-Ang, S-Ang/F, S-Ang/V and S-Ang/P. This result indicates the inclination in PGs in experiencing a remarkable intensity of anger as an emotional state at a particular time. Moreover PGs showed a disposition to perceive a wide range of situations as annoying or frustrating and a tendency to respond to such situations with elevations in anger as showed by higher scores on all trait-anger scales: T-Ang, T-Ang/T and T-Ang/R. Furthermore PGs showed higher expression of angry feelings both verbally or physically (AX-O), higher global levels of anger expression highlighted by AX Index, lower levels of control on the outward expression of angry feelings, (AC-O) and lower attempts to control angry feelings by calming down or cooling off (AC-I), (Table 2). The MANOVA test (using the Pillai's criterion) with the TAS-20 scores revealed a significant effect between groups accross each scale; specifically PGs reported higher levels of alexithymia (total score), difficulty in identifying feelings (first scale), difficulty in describing feelings to others (second scale) and an externally-oriented thinking (third scale) (Table 3).

2.6.2 Alexithymia, anger and severity of gambling disorder

The association between alexithymia, anger and severity of gambling disorder was explored using a bivariate Pearson's correlation. This indicated that alexithimia, "state-anger" and "trait-anger" are all positively correlated with each other (Table 4). Severity of gambling behaviour was positively correlated with alexithymia scores and anger levels, so that when anger or alexithymia scores increased so did the severity of gambling behaviour.

2.6.3 Gambling behaviour and anger after controlling for alexithymia

The occurrence of a relationship between anger expression and gambling behaviour apart from the relationship between gambling and alexithymia was revealed by a hierarchical multiple regression analysis performed on all subjects in both groups, in which alexithymia score was added on the first step (Model 1), while trait-anger and state-anger were added on the second step (Model 2). Multicollinearity was assessed using the variance inflation factor (VIF). VIF scores ranged

between 1.000 and 1.417 and the larged condition index was less than 10, suggesting a lack of significant multicollinearity (Belsley 1991). Table 5 shows the results of the hierarchical multiple regression: alexithymia was a significant predictor of SOGS scores, accounting for 20.9% of the variance (Model 1); notably, the addition of anger scores in the second step significantly increased by 18.9% the explained variance in SOGS scores, contributing significantly to the prediction of pathological gambling behaviour (Model 2).

2.6.4 Gender and anger

In order to evaluate whether gender plays a role on anger expression in gambling behaviour, a hierarchical multiple regression analysis including gender was performed on all subjects in both groups. Table 6 shows the lack of significant interactions between gender and anger in gambling (Model 3), indicating that gender did not significantly increase the explained variance in anger scores, neither did the interaction between predictors and gender.

Table 1: *Descriptive statistics of the sample by gender, age and years of education*

FACTOR	PATHOLOGICAL GAMBLERS (n=100) Frequency (%)	HEALTHY CONTROL GROUP (n=100) Frequency (%)	TEST Pearson's Chi Squared
SEX			
Male	88 (83.3)	82 (80.0)	.235NS
	PATHOLOGICAL GAMBLERS (n=100) Mean (St. Dev.)	HEALTHY CONTROL GROUP (n=100) Mean (St. Dev.)	TEST ANOVA
MEAN AGE (years)	41.53 (10.96)	41.27 (13.46)	.22NS
MEAN EDUCATION (years)	11.35 (2.66)	12.95 (2.77)	2.429 NS

Note. NS Non significant; *p < .05; **p < .01; ***p < .005; ****p < .001.

Table 2: *STAXI-2 scores between groups*

FACTOR	PATHOLOGICAL GAMBLERS (n=100) Mean (SD)	HEALTHY CONTROL GROUP (n=100) Mean (SD)	TEST MANOVA F
State Anger (S-Ang)	54,50 (14.20)	45,98 (5.99)	30.535****
Feeling Angry (S-Ang/F)	56.40 (15.1)	47.08 (7.77)	29.980 ****
Feel Like Expressing Anger Verbally (S-Ang/V)	54.37 (14.69)	45.96 (8.504)	24.525 ****
Feel Like Expressing Anger Physically (S-Ang/P)	49.2 (10.809)	44.72 (3.01)	15.936****
Trait Anger (T-Ang)	49.94 (10.85)	42.38 (7.69)	32.249****
Angry Temperament (T-Ang/T)	50.28 (9.79)	43.20 (6.4007)	36.596****
Angry Reaction (T-Ang/R)	49.54 (9.95)	43.80 (9.33)	17.686****
Anger Expression-Out (AX-O)	51.90 (9.76)	48.68 (6.508)	7.527**
Anger Expression-In (AX-I)	50.54 (10.54)	49.72 (10.22)	.312 NS
Anger Control-Out" (AC-O)	44.24 (10.54)	50.18 (7.59)	20.888****
Anger Control-In (AC-I)	48.96 (8.55)	54.78 (9.09)	21.737****
Anger Expression Index (AX Index)	52.62 (10.35)	45.56 (7.79)	29.665****

Note. NS Non significant; *p < .05; **p < .01; ***p < .005; ****p < .001.

Table 3: *TAS-20 scores between groups*

FACTOR	PATHOLOGICAL GAMBLERS (n=100) Mean (SD)	HEALTHY CONTROL GROUP (n=100) Mean (SD)	TEST MANOVA
Total Score	51.15 (12.81)	42.33 (11.51)	26.053****
Difficulty Identifying Feelings (DIF)	43.98 (19.105)	38.60 (15.39)	4.808*
Difficulty Describing Feelings (DDF)	58.55 (19.54)	47.10 (19.14)	17.525****
Externally Oriented Thinking (EOT)	52.605 (14.23)	42.59 (11.98)	28.932****

*Note. NS Non significant; *p < .05; **p < .01; ***p < .005; ****p < .001.*

Table 4: *Bivariate Pearson's correlation between SOGS, TAS-20 and STAXI-2*

FACTOR	SOGS	TAS-20 TOTAL SCORE	STAXI-2 STATE-ANGER	STAXI-2 TRAIT-ANGER
SOGS	1	.457**	.454**	.501**
TAS-20 TOTAL SCORE	.457**	1	.490**	.297**
STAXI-2 STATE-ANGER	.501**	.297**	1	.368**
STAXI-2 TRAIT-ANGER	.454**	.490**	.368**	1

*Note. NS Non significant; *p < .05; **p < .01; ***p < .005; ****p < .001.*

Table 5. *Hierarchical multiple regression analysis predicting pathological gambling behaviour from anger controlling for alexithymia*

FACTOR	Model 1					Model 2				
	β	*t*	*p*	*r*	*sr*	*β*	*t*	*p*	*r*	*sr*
TAS-20 Total Score	,457	7.233	.000	.457	.457	.255	3.923	.000	.457	.220
STAXI-2 State- Anger						.352	5.778	.000	.501	.324
Trait- Anger						.199	2.980	.003	.454	.167
Model R^2	,209					,398				
R^2 Change	,205					,386				
F	(1,198) =	52.319****				(2,196)=	20.457****			

*Note. NS Non significant; *p < .05; **p < .01; ***p < .005; ****p < .001.*

Table 6. *Hierarchical multiple regression analysis predicting pathological gambling behaviour from anger controlling for gender*

FACTOR	Model 1					Model 2					Model 3				
	β	*t*	*p*	*r*	*sr*	*β*	*t*	*p*	*r*	*sr*	*β*	*t*	*p*	*r*	*sr*
STAXI-2 State-Anger	,375	4,163	,000	,429	,367	,384	4,246	,000	,429	,374	,363	4,016	,000	,429	,350
Trait-Anger	,256	2,837	,006	,334	,250	,244	2,694	,008	,334	,237	,234	2,603	,011	,334	,227
Gender						,095	1,064	,290	,092	,094	,090	1,025	,308	,092	,089
Interaction											-,153	-1,726	,088	-,233	-,150
Model R^2	,246					,255					,278				
R^2 Change	,231					,232					,247				
F	(2,97) =	15,842***				(1,96) =	1,133NS				(1,95)=	2,978NS			

*Note. NS Non significant; *p < .05; **p < .01; ***p < .005; ****p < .001.*
Gender with male coded as 1 and female coded as 2.

2.7 DISCUSSION

This research has investigated the occurrence of anger and alexithymia in a group of treatment-seeking PGs and compared them with HCs. Moreover we have tested whether anger could be predictive for gambling severity, after controlling for the role of alexithymia, taking into account the role of gender on its expression. Our data reveal a significant higher presence of alexithymia in PGs, compared with HCs. This is consistent with several reports on different typologies of problematic gamblers confirming the relationship between involvement in gambling and alexithymia (Bonnaire et al. 2013; Mitrovic & Brown. 2009; Maniaci et al. 2015). Furthermore it is well-known that high alexithymia levels are associated with higher craving in substance use disorder. Indeed, alexithymia scores predict more severe tobacco craving during nicotine

withdrawal (Sutherland et al. 2013). Moreover, studies have shown that alexithymic subjects report significantly higher levels of compulsive drinking urges and behaviour, compared to the non-alexithymic group (Thorberg et al. 2011). Furthermore, alexithymia-related deficits in emotion identification appear to be positively associated with craving levels reported in response to methamphetamine cues (Saladin et al. 2012). Hence, considering the similarities between pathological gambling and drug addiction, the presence of high alexithymia levels could be viewed such as a risk factor for a great probability of losing control and surrendering to gambling craving (Toneatto et al. 2009). An alteration in the emotional regulation process could lead PGs to lose control in gambling more easily. On the contrary a good awareness of own feelings and a positive proneness to the expression of emotions could help PGs to improve control of the impulse to gamble. Therefore these data suggest clinicians to give an appropriate importance to the evaluation of alexithymia in PGs during the assessment process and also during the treatment.

Another considerable outcome of this study is the observation that PGs display higher state-anger and trait-anger levels, compared to HCs. Our results also show a clear assocation between anger an pathological gambling, consistent with findings in different psychiatric conditions, including affective disorders, substance use disorders, post-traumatic stress disorder and sexual behaviour (Demirbas et al. 2011; Gardner & Moore 2008; Olatanji & Lohr 2005; Scimeca et al. 2013; Wilkowski & Robinson 2008). The elevation of state-anger scale reveals an inclination to experience anger during the testing situation, and to express it both verbally and physically. Moreover, high trait-anger levels suggest a disposition to perceive a wide range of situations as annoying or frustrating, and a tendency to react angrily to such contexts. PGs are inclined to experience frequent anger at varying intensity, that is often accompanied by related negative emotions such as envy, resentment, hate and disgust. They become angry or agitated when criticized, receive negative feedback, or believe that someone is displaying inappropriate behaviour towards them. Furthermore, the anger expression process appears to be characterized by dysfunctional modalities; PGs express anger outwardly in a negative and poorly controlled manner,

trying sometimes to suppress anger inwardly when they are furious. This remarkable presence of anger, together with the risk of suicide attempts represent a feature that is shared by pathological gambling and other addictive behaviours (Hwang et al. 2014). Suicidal thoughts or attempted suicide behaviours are often reported by patients suffering from pathological gambling (Hansen & Rossow 2008; Thon, et al. 2014). Furthermore, there is a wellknown association between dysfunctional anger expression and suicide risk in different psychiatric disorders (Horesh et al. 1997; Miller & Lynam 2006). Hence our findings could suggest to take into account suicide risk in treatment seeking PGs, especially when they are characterized by higher state-anger and trait-anger levels. This is also important for PGs that are following an antidepressant therapy (Aursnes et al. 2005).

A further aim of the present study has been to asess the correlation between state-anger, trait-anger, alexithymia scores and severity of gambling behaviour. Our data shows that subjects with dysfunctional modality of anger expression display a worst gambling behaviour, suggesting that a greater alteration in the emotional regulation process may play a role in the severity of the addictive behaviour. Moreover, when the contribution of anger in gambling behaviour was evaluated after controlling for alexithymia, a significant occurrence of anger in PGs, beyond the relationship between alexithymia and gambling behaviour, was recorded. This result suggests that in the assessment of PGs, anger expression should be viewed as a considerable step of the clinical evaluation, particularly in those subjects who display impulsivity and suicide thoughts. Several studies show that anger is a sex related variable (Fox et al. 2008); however, although men and women can express anger through different modalities, our results do not support an evidence of gender differences. The small number of females in our sample could be an explanation for this unexpected result. Indeed the majority of PGs recruited were treatment-seeking and predominantly males. However this imbalance between men and females mirror the National statistical reports showing that male PGs represent approximately 80% of the treatment seeeking sample for gambling problems (Serpelloni 2013). On the other hand the strength of this study consists in the evaluation

of the role played by anger in the severity of gambling, which has been an underestimated parameter so far. An additional value of this research consists in carrying out the analysis in an homogeneous groups of PGs, at the same stage of treatment and compared them with a proper control group, matched for age, gender and education.

2.8 CONCLUSIONS

This study shows that subjects diagnosed with gambling disorder are characterized by pathological anger levels and alexithymia. Particularly, PGs show difficulty in identifying and describing feelings, an externally-oriented thinking and high state-anger and trait-anger levels. The alteration in the emotional regulation process together with higher anger levels are associated to a worsening in gambling behaviour. Anger is a psychological trait present in PGs independently from the relationship between gambling behaviour and alexithymia. The current findings contribute to an improved understanding of the complexity of the factors that are implicated in gambling disorder, and to a better orienting of the assessment process towards the evaluation of anger expression and alexithymia. This further diagnostic step could promote an effective and tailored treatment protocol, preventing self-defeating behaviours and reducing dropout from the therapies.

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PART 3

IMPULSIVITY AND STRESS RESPONSE IN PATHOLOGICAL GAMBLERS DURING THE TRIER SOCIAL STRESS TEST

3.1 INTRODUCTION

Despite gambling disorder is thought to be influenced by neurobiological factors it isn't clear yet if a specific involvement of the hypothalamic-pituitary-adrenal axis and of the sympathetic nervous system exist in gambling disorder. This study aims at investigating the effect of the Trier Social Stress Test on cortisol and on interbeat interval in relation to impulsivity measure in a sample of male pathological gamblers, compared to a control group.

3.2 BACKGROUND

Clinical and neuropsychological studies show that impulsivity is an important factor which contributes to the onset and worsening of gambling disorder (Blanco et al, 1996; Steel & Blaszczynski, 1998; Van Holst et al, 2010b; Verdejo-Garcia et al, 2008). Impulsivity can be defined as a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions. The strong presence of impulsivity lead subjects to be highly responsive to immediate positive reinforcement but rather insensitive to long term negative consequences. Compared to healthy controls, PGs display increased levels of impulsivity (Marazziti et al, 2014) and interestingly compared to alcoholics and cocaine misusers, gamblers scored significantly higher on impulsivity and inability to resist craving (Castellani & Rugle, 1995). However it isn't a pathological gambling-specific impulsivity profile compared to other mental disorders (Kraplin et al., 2014). Furthermore high impulsivity is considered as an important factor for treatment failure in pathological gambling (Leblond et al, 2003). Moreover impulsivity is related to diminished decision-making process and higher risky behaviour. Indeed impulsive subjects, such as PGs, learn more slowly to choose from the advantageous decks of the Iowa Gambling Task

(Cavedini et al, 2002; Zermatten et al, 2005) preferring in their decisions smaller immediate rewards to larger delayed rewards (Alessi & Petry, 2003; Petry & Carasella, 1999).

Different studies reported increased physiological arousal in recreational gamblers while engaging in gambling related activities, as a result of measuring heart rate and hypothalamic-pituitary-adrenal axis (HPA) responses (Coventry & Constable, 1999, Krueger et al, 2005; Wulfert et al, 2008). Meyer et al. reported that alterations in stress hormones accompany the activation of cardiovascular activity during gambling in regular gamblers. Gambling produces a moderate heart rate elevation, which persists following termination of the game and an increased level of salivary cortisol (Meyer et al, 2000). Nevertheless when compared with non-problem gamblers, problem gamblers do not show significant differences in plasma cortisol response during casino gambling (Meyer et al, 2004). Moreover no significant differences in baseline cortisol were found between recreational and PGs during a cue reacitivy paradigm. Measuring cortisol before and after the task, recreational gamblers showed significantly increased salivary cortisol levels compared to PGs suggesting that pathological gambling is associated with a hypocortisolemic response to gambling stimuli, due to a chronic exposure to gambling (Paris et al, 2009). Thus the continued exposure to "*exciting*" activities such as gambling could lead to an overstimulation of the HPA axis and of the sympathetic nervous system in PGs and this could explain the lower stress response in PGs during the cue reactivity paradigm highlighted in the study described above or even during the execution of the Iowa Gambling Task (Goudriaan et al, 2006). Geisel et al hyphotisized that alterations of HPA axis activity might represent a common mechanism of pathology between substance dependence and behavioural addictions. The Authors investigated plasma levels of the HPA axis hormones copeptin, ACTH and cortisol in patients with pathological gambling and internet use disorder in comparison with healthy controls. However, contrary to their hypothesis the results revealed no significant alterations of the HPA axis among the groups. Cortisol plasma levels negatively correlated with the severity of gambling disorder indicating that patients with a higher severity of

gambling disorder showed lower plasma cortisol levels (Geisel et al, 2015). Remains unclear if HPA axis response could negatively correlate also with the duration of pathological gambling. .

Given the involvement of HPA-axis related to gambling exposure, and previous studies that indicate that regular gamblers have a higher stress response during gambling (Meyer et al. 2000), but a lack of studies on HPA-axis stress responsivity in PGs, this study focuses on the question whether PGs have an abnormal HPA-axis stress reactivity during a social stress test. We hypothesize to find differences between groups regarding the physiological stress response to the psychological stress test Then considering the evidence suggesting that hypocortisolism may be a consequence of exposure to chronic stress (Heim et al. 2000) we hypothesize to find a negative correlation between physiological parameters related to the stress response and the duration of gambling disorder . Specifically, we hypothesize that a higher duration of the disorder would been related to a lower baseline salivary cortisol and a lower heart rate. Thirdly, considering data concerning the relationship between neuroendocrine variables and impulsivity showing higher heart rate levels in high-impulsivity blackjack players but the lack of a comparison with a control group (Krueger el al. 2005) we investigated the effect regarding the interaction between impulsivity and group (PGs – HCs) on HPA axis and on cardiovascular activity.

3.3 MATERIALS AND METHODS

3.3.1 Participants

A total of 26 PGs and 18 HCs, ranging from 19-58 years old, participated in this study. PGs were recruited from a local addiction treatment center where they received cognitive behavioral treatment for pathological gambling. HCs were recruited through advertisements in local newspapers. Because most treatment-seeking PGs are men, only male participants were included in the study. Exclusion criteria for both groups were: lifetime diagnosis of schizophrenia or psychotic episodes; diagnosis of manic disorder (CIDI, section F), obsessive compulsive disorder (CIDI, section E), alcohol use disorders (CIDI, section J), substance dependent disorder (CIDI, section L)

or post-traumatic stress disorder (CIDI, section K); treatment for mental disorders other than pathological gambling in the past 12 months; use of psychotropic medication; difficulty reading Dutch; IQ below 80 (measured by the Dutch Adult Reading Test; Schmand et al., 1991); age under 18 years; positive urine screen for alcohol, amphetamines, benzodiazepines, opioids or cocaine; history or current treatment for neurological disorders, major internal disorders, brain trauma, or exposure to neurotoxic factors. In addition, HCs were excluded if they gambled more than twice a year. To obtain a measure of subjects' global information processing speed, the subscales Digit span and Number-Letter sequencing from the Wechsler Adult Intelligence Scale-Revised (WAIS-R) were administered and were combined in a composite score for information processing speed (Wechsler, 1981). The study was approved by the ethical review board of the Academic Medical Centre, and all participants gave written informed consent and all measures were administered under respect of privacy. Participants were reimbursed with 50 Euros transferred to their bank account following participation.

3.3.2 Measure of stress induction

A modified version of the "Trier Social Stress Test" (TSST) was used as psychosocial stressor. TSST is one of the most reliable and standardized protocol for studying the stress hormone reactivity (Kirschbaum et al., 1993). In the TSST, participants have to perform two different tasks in front of a selection committee and a video camera. The committee consists of three experimenters introduced as being trained in "behavioural observation". Participants are told that their performance is recorded on video to later analyze voice pitch and nonverbal behaviour. In the TSST version that we used, first of all the subject has to wait 45 minutes upon arrival of the psychologists. Then the subject gets instructions to prepare a free speech, about any theme he/she wants. Before preparing, the subject has to fill in a questionnaire. The subject gets 10 minutes to prepare the speech and the speech has to take 5 minutes. After the subject has finished the speech, he or she has to do an arithmetic task (subjects were asked to make subtractions of 7 from 1029, and

in case no errors were made during the first 5 subtractions, a switch was made to subtractions of 13). The committee does not provide any further feedback but acts in a very cold and reserved manner. The recovery period contains 45 minutes after the arithmetic task is completed. The TSST has been shown to lead to a robust increase in cortisol through the activation of the HPA axis and sympathetic nervous system (Brkic et al, 2015; Dickerson & Kemeny, 2004; Inagaki et al., 2015; Kirschbaum and Hellhammer, 1994).

3.3.3 Measures of stress response

3.3.3.1 HPA axis response

Cortisol was collected six times, but in this study we considered only the first five measurements, because a considerable amount of the subjects were missing the last measurement, 40 minutes after the stress task (see Table 1). The Kirschbaum's protocol was used for collecting cortisol (Kirschbaum et al, 1993). Cortisol levels were determined from saliva samples representing the unbound biologically active hormone fraction. Saliva cortisol is highly correlated with serum free and total cortisol levels and has been shown to be independent of saliva flow rate. The non-invasive sampling makes saliva steroid measurement the method of choice for investigations of stress effects on cortisol. For easy and hygienic sampling of saliva, the Salivette sampling device (Sarstedt, Rommelsdorf, Germany) was employed. Samples were stored at -20°C until being assayed. For cortisol analysis, a time resolved fluorescence immunoassay was used. Intra- and interassay precision was less than 6 and 8%, respectively.

3.3.3.2 Sympathetic Nervous System response

Throughout the TSST electrocardiogram (ECG) signal was recorded continuously to monitor the heart rate variability. The Vrije University- Ambulant Monitoring System (AMS) 5fs-SCL version (Skin Conductance Level) was connected 30 minutes prior to initiation of the stress task. Seven active Ag/AgCL electrodes (10 mm, Ultra trace) were used. The first electrode was placed slightly below the collar bone, 4 centimeters to the right of the sternum. The second was

placed between the lower two ribs, just right of the sternum. At the jugular notch, just above the sternum, the third electrode was placed, while the fourth electrode was placed at the xiphoid process, just under the sternum, both in the medial line. Finally the sixth and seventh electrodes were placed dorsally, on the spine, 3 centimeters above electrode four and 3 centimeters below electrode five respectively. The ECG signal was led into a differential amplifier with an input impedance higher than 1 MO. The amplified ECG was then passed through a band pass filter at 17 HZ after which it was used for R-peak triggering. At each R-peak, a millisecond counter was read and reset, yielding inter beat interval (IBI). Likewise for the salivary cortisol we considered only the first five IBI measurements, because many subjects were missing the last measurement (see Table 2).

3.3.4 Psychological measures

3.3.4.1 Gambling Behaviour Assessment

All subjects completed the South Oaks Gambling Screen (SOGS). The SOGS is a 20 items questionnaire that measures gambling behaviour through questions on participant's history of gambling, the frequency at which the person engages in these behaviours, and obstacles that gambling may have posed in the participant's life. The total score on the SOGS ranges from 0 to 20 (scores from 5 indicates probable pathological gambling) (Lesieur, & Blume, 1987).

3.3.4.2 Gambling diagnosis and exclusion criteria

To assess the diagnostic criteria for a DSM-IV-TR diagnosis and to evaluate the exclusion criteria of this study, it was used the Composite International Diagnostic Interview (CIDI). CIDI is a comprehensive standardized diagnostic interview designed for assessing mental disorders according to the DSM-IV (WHO, 1997) .

3.3.4.3 Impulsivity

To evaluate impulsiveness we used the Barratt Impulsiveness Scale, 11th version (BIS-11) (Barratt, 1985). The BIS-11 is a self-report questionnaire, which contains 30 questions that need to be scored on a scale from 1 to 4 (1=rarely/never; 2=occasionally; 3=often; 4=almost

always/always). Factor analysis includes 6 first order factors (attention, motor impulsiveness, self-control, cognitive complexity, perseverance and cognitive instability) and 3 second order factors (attentional impulsiveness, motor impulsiveness and non-planning impulsiveness). The BIS-11 total score indicates the level of impulsiveness. The higher the BIS-11 total score, the higher the impulsiveness level is. The questionnaire contains statements that indicate impulsive behaviour ('I do things without thinking') and statements that indicate non-impulsive behaviour ('I am self-controlled'). The BIS-11 is the most frequently used self-report measure of impulsivity.

3.3.5 Procedure

After the informed consent was written, participants filled out questionnaires. Then they started to be subject to the modified version of the TSST described above. During the TSST salivary cortisol and heart rate variability were collected. All testing sessions took place between 1 PM and 4 PM to ensure that there were no large variations in cortisol secretion due to circadian rhythm (Kudielka et al., 2004)

Table 1. Procedure of salivary cortisol measurement

SALIVARY CORTISOL MEASUREMENTS	TSST STEPS	TIME (minutes)
1	Baseline	-20
2	Start preperation	0
3	Start speaking task	10
4	End cognitive task	18
5	20 minutes after end stress task	40
6	40 minutes after end stress task	60

Table 2. Procedure of IBI interval extraction

IBI INTERVAL EXTRACTION	TSST STEPS	TIME (minutes)
1	Baseline	-20
2	Start preperation	0-2
3	Start speaking task	10-12
4	End cognitive task	18-20
5	20 minutes after end stress task	40-42
6	40 minutes after end stress task	60-62

3.4 STATISTICAL ANALYSIS

One-way analysis of variance (ANOVA) was used to evaluate significant differences between PGs and HC in age, BIS-11 and SOGS scores. A repeated measures ANOVA with "*time*"

as within-subjects factor and "*group*" as between-subjects factor for both collected stress measures (salivary cortisol and IBI) was performed. Greenhouse-Geisser corrected p-values were used when appropriate. Partial eta-squared (*ηp2*) was used as a measure of effect size. Bivariate Pearson's correlation was used to verify a correlation between stress measures and the duration of the disorder. To explore the relationship between impulsivity, gambling behaviour and the physiological stress measures during the TSST we used the myxed model analysis. All analysis were performed with an alpha of 0.05. Statistical analysis was conducted on SPSS for Windows 22.0.

3.5. RESULTS

3.5.1 Sample characteristics and differences in impulsiveness

Table 3 includes the descriptive data of both samples; no significant statistical differences between groups in age were found. As expected we found significant differences between groups regarding SOGS scores ($p<.001$) but not in the total score of the BIS-11.

3.5.2 Stress reactivity during and after the TSST

A significant main effect of time was found with the repeated measures ANOVA, meaning that the TSST significantly activated the HPA axis through an increase of salivary cortisol ($p<.001$) and the sympathetic nervous system through a modification of the interbeat interval ($p<.001$). However we found no significant difference between groups regarding the increased cortisol or the interbeat interval during or after the application of the TSST (Table 4) (Figure 1).

3.5.3 Stress response and "*duration*" of the disorder

The association between the duration of the gambling disorder and the physiological stress response to the TSST was explored using a bivariate Pearson's correlation. Consistently with our hypothesis we found a negative correlation between the duration of pathological gambling and baseline cortisol levels ($r = -.459$; $p<.05$). Therefore increasing duration in gambling addiction appears related to lower baseline cortisol levels (Table 5). Contrary to our hypothesis we found no

significant correlations between the duration of the disorder and sympathetic nervous system activity (Table 6).

3.5.4 Impulsivity and physiological stress response

The relationship between impulsivity and physiological responses during the TSST, and whether this relation differed between PGs and HCs was investigated through a mixed model analysis. There was a significant main effect of impulsivity on IBI, ($F(1, 40) = 9.353$, $p < .005$) and on salivary cortisol ($F(1, 40) = 7.409$, $p < .05$) during the stress test. Furthermore we found no significant effects regarding the interaction between impulsivity and group on IBI or cortisol levels. (Figure 2).

Table 3: *One-Way ANOVA between groups by age SOGS and BIS-11 scores*

FACTOR	PATHOLOGICAL GAMBLERS (n=25) Mean (SD)	HEALTHY CONTROLS (n=16) Mean (SD)	TEST One-Way ANOVA F
AGE	36.35 (12.02)	39.38 (10.66)	.692 NS
SOGS	10.92 (3.26)	0.05 (0.23)	197.757****
BIS-11	55.61 (6.34)	51.55 (7.49)	3.756NS

Note. NS Non significant; *p < .05; **p < .01; ***p < .005; ****p < .001.

Table 4: *Repeated measures ANOVA for cortisol and IBI*

FACTOR	F	df	MSE	p	*ηp2*
Cortisol: time	18.142	1.501	994.816	****	.302
Cortisol: time x group	.269	1.501	14.724	NS	.006
IBI: time	65.309	2.712	263315.38	****	.609
IBI: time x group	.795	2.712	3206.927	NS	.019

Note. NS Non significant; *p < .05; **p < .01; ***p < .005; ****p < .001.

Table 5: *Bivariate Pearson's correlation between "duration" of the disorder and salivary cortisol*

FACTOR	1	2	3	4	5
DURATION	-.456*	-.350 NS	-.253 NS	-.237 NS	-.166 NS

Note. NS Non significant; *p < .05; **p < .01; ***p < .005; ****p < .001

Table 6: *Bivariate Pearson's correlation between "duration" of the disorder and IBI*

FACTOR	1	2	3	4	5
DURATION	-.020 NS	-.002 NS	-.118 NS	-.060 NS	-.095 NS

Note. NS Non significant; *p < .05; **p < .01; ***p < .005; ****p < .001.

Table 7: *Myxed model analysis for impulsivity and cortisol and impulsivity and IBI*

FACTOR	F	df	p
Impulsivity: cortisol	7.409	1.40	*
Impulsivity: cortisol x group	.027	1.40	NS
Impulsivity: IBI	9.353	1.40	***
Impulsivity: IBI x group	.031	1.40	NS

Note. NS Non significant; *p < .05; **p < .01; ***p < .005; ****p < .001.

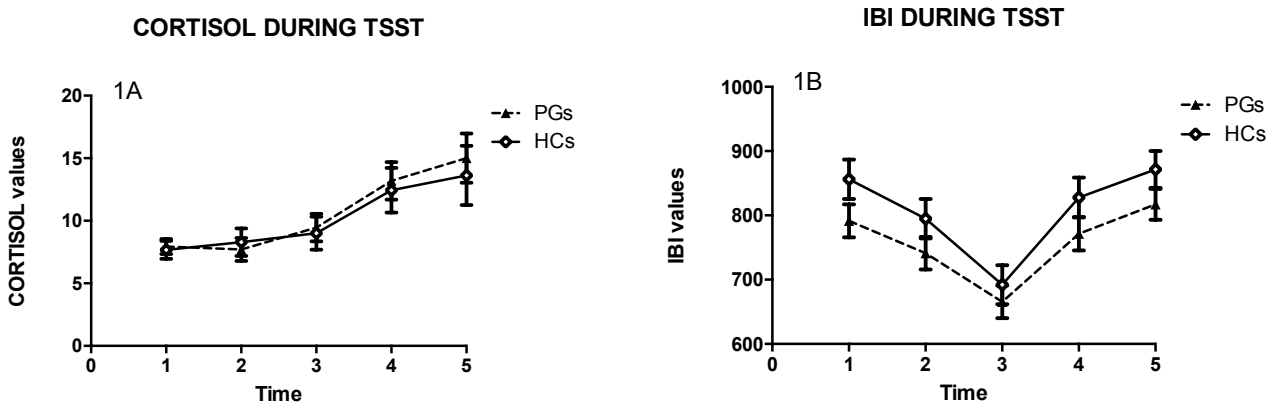

Figure 1 (A,B). Cortisol (Fig. 1A) and IBI (Fig. 1B) levels at baseline, during stress induction, and after cessation of the TSST in PGs and HCs

3.6 DISCUSSION

This research has investigated the effects of the TSST on HPA axis and on sympathetic nervous system response in relation to impulsivity in a sample of male PGs, compared to HCs. We studied the increase of salivary cortisol and the interbeat interval in PGs during and after the social stress test and compared this to the control group response. Contrary to our hypothesis the TSST produced a significant increase of the salivary cortisol and of the interbeat interval without significant differences between groups. Although PGs showed a modification in the physiological stress response during the TSST, these changes did not differ from the control group. This outcome fits with previous studies, which revealed no significant specific HPA axis response to casino gambling in regular gamblers compared to non-regular gamblers (Meyer et al, 2004) and it is important because it shows that PGs have a similar physiological stress response to HCs also during a non gambling-related task such as the TSST.

Our second hypothesis was partially confirmed because we found a significant negative correlation between baseline cortisol and duration of the gambling disorder but not between

baseline IBI and duration. Different studies highlighted an association between the severity of psychiatric disorders and cortisol levels, such as in post-traumatic stress disorder (Yehuda et al, 1996), generalized anxiety disorder (Steudte et al, 2011) and pathological gambling (Geisel et al, 2015). Our outcome appears relevant because it shows that a higher duration of the disorder is related to lower salivary cortisol levels. This correlation could be interpreted as a response in PGs to chronic distress caused by enduring gambling behaviour, also confirming the involvement of HPA axis in pathological gambling. Indeed chronic and repeated stressors can lead to one or more forms of HPA axis dysregulation, altering appropriate cortisol secretion and affecting end-organ function. Evidence suggests that hypocortisolism may be a common consequence of exposure to severe acute stress and chronic intermittent stress. Several studies have confirmed states of hypocortisolism in patients chronically exposed to stressful environments, those with unpredictable schedules and in those with traumatic early life experiences (Gunnar & Vazquez, 2001; Heim et al, 2000). A possible explanation for this result suggests that under the influence of chronic stress, the initial adaptive hypercortisolism response transforms over time into a self-preserving hypocortisolism state in order to protect the metabolic machinery, and most importantly, the brain (Hellhammer & Wade, 1993). Likewise several disorders related to stress, such as, fibromyalgia, rheumatoid arthritis and asthma, it could be possible that also in pathological gambling the repeated stress in which the gambler is involved can produce an alteration of the HPA axis finally leading to an hypocortisolism. Furthermore the persistent hypocortisolism in PGs, may promote an increased vulnerability for the development of physical consequences, such as high-stress sensitivity, chronic fatigue and chronic pain (Fries et al. 2005)

Concerning the last hypothesis of this study we found a significant main effect of impulsivity on salivary cortisol and IBI. However this effect appears not directly related to the gambling disorder, because no significant differences between groups were founded. Higher impulsivity subjects revealed significantly higher salivary cortisol levels throughout the social stress test and higher interbeat interval. Thus impulsivity, independently from the gambling disorder,

appears related to an increased HPA axis activity and a decreased cardiovascular response during the TSST. Even it is not possible undenstanding the nature of the causal relationship between physiological stress response and impulsivity this outcome confirms the relationship highlighted in other studies between impulsivity and cardiovascular response during a stress task (Allen et al. 2009).

This combination of high impulsivity and physiological stress response could lead to different effects depending on specific pathologies. In pathological gambling it is well-known that reduced impulse control leads to impulsive decision making without an advantageous risk balancing (Brand et al, 2005; Goudriaan et al, 2005). Therefore, this outcome reveal the importance of studying impulsivity in relation to stress reactivity independently from the presence of a specific disorder, considering the stress response of the high-impulsivity subjects such as a possible risk factors for the onset of different disorders.

The present study has some limitations. Firstly, the sample size was too small to draw final conclusions regarding the involvement of the HPA axis and of the sympathetic nervous system in pathological gambling. Secondly, only male participants were included, thus limiting the generalizability of our results. However the strenghts of this study are considerable. As far as we know this study is the first to examine physiological stress measures in response to a psychological stress test such as the TSST in PGs, compared to a control group. Furthermore we found that a longer duration of the disorder is related with a decrease of baseline cortisol. This result is probably due to a chronic stimulation of the HPA axis in PGs thus confirming an involvement of the hormonal stress system in pathological gambling. Moreover, we highlighted a main effect of impulsivity in the stress response to the TSST not directly related to the gambling disorder.

In conclusion gambling disorder appears related to HPA axis activity and particularly to a lower availability of cortisol in gamblers with a longer duration of the disorder. Moreover the association among the physiological stress response and impulsivity appears to be relevant in the understanding of several facets of pathological gambling, giving to the clinicians the possibility to

organize efficacious therapeutic strategies, reducing the risk of relapse. Further studies need to investigate the relation between impulsivity and physiological stress response in PGs, recruiting a larger sample and including females problem gamblers.

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PART 4

NEUROFUNCTIONAL ASSESSMENT OF SALIENCE ATTRIBUTION AND INHIBITORY CONTROL IN PATHOLOGICAL GAMBLERS DURING A GO-NOGO TASK

4.1 INTRODUCTION

In the fourth part of this thesis I present data regarding the assessment of pathological gambling. Starting from the psychodiagnostic assessment, we upgraded to a biological investigation to complete with a neurofunctional study. In details in this last part we investigated the salience attribution and the inhibitory control in pathological gamblers tested in a Go-NoGo task during a functional magnetic resonance sesssion.

4.2 BACKGROUND

A strong neurobiological model for substance dependence, the Impaired Response Inhibition Attribution (I-RISA), postulates that repeated drug use leads to a series of adaptations in neuronal circuits involved in memory, motivation, and cognitive control. This results in an enhanced salience for drug-related stimuli and it is associated with a decreased salience for natural reinforcers (Volkow et al., 2003). Although the I-RISA model is based on findings in substance dependent subjects, converging evidence suggest that this model could also be applied on pathological gambling (Petry, 2006; Potenza, 2006; van Holst et al., 2010). Studies on salience attribution towards gambling cues in pathological gamblers (PGs) reported enhanced BOLD responses in the amygdala, cingulate cortex, dorsolateral prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex (VLPFC) (Crockford et al., 2005; Goudriaan et al., 2010), similar to the enhanced BOLD responses to drug-related pictures or movies in alcohol and drug dependent subjects (Braus et al., 2001; Wrase et al, 2007). Furthermore, diminished sensitivity towards monetary wins and losses as observed in substance dependent disorders (Beck et al., 2009) has also been reported in PGs (de Greck et al, 2010; de Ruiter et al., 2008; Reuter et al., 2005). Cognitive control and impulse regulation correlate with proper prefrontal cortex functioning, in particular the inferior frontal

cortex (IFC), anterior cingulate (ACC) and DLPFC (Aron et al., 2004; Casey et al., 1997; Rubia et al., 2001; Watanabe et al., 2002). Diminished IFC, ACC and DLPFC activity associated with impaired response inhibition occur in individuals with a substance use disorder (Fu et al., 2008; Hester and Garavan, 2004). Hovewer, other studies found opposite results, highlighting an increased activity in IFC, ACC and DLPFC in the substance dependent groups together with a similar response inhibition performance (Roberts and Garavan, 2010; Tomasi et al., 2007). These latter findings were interpreted as indicative of a compensatory brain response in substance dependent individuals to achieve a similar level of performance as controls. Impaired response inhibition were reported in behavioural studies in PGs, e.g., increased cognitive interference on the Stroop task, and diminished inhibition in stop-signal tasks (Goudriaan et al., 2008; MacKillop et al., 2006). Similar to the literature in substance use disorders, some studies failed to observe behavioural differences between problem gamblers and healthy controls (Kertzman et al., 2006; Kertzman et al., 2008). Using the Stroop task during functional magnetic resonance imagine (fMRI), Potenza et al., compared the response inhibition between PGs and controls, highligthing a diminished VLPFC activity in the clinical group (Potenza et al., 2003). As far as we know only a few studies have analyzed the interaction between cognitive control and salience attribution in PGs (van Holst et al., 2012). Van Holst et al. used a Go-NoGo task consisting in four blocks that contained positive, negative, neutral, or gambling-related pictures. The results of this study showed slower reaction times in PGs compared to healthy controls (HCs) and less impulsive errors during the gambling-related block. Regarding the salience attribution the study showed in PGs more activity in left DLPFC, right ventral striatum and right ACC when compared to HCs on the contrast "Gambling Go vs Neutral Go". Furthermore PGs showed more activity while watching positive Go pictures vs Neutral Go pictures in left DLPFC and left IFC and more activity was revealed in PGs on the Negative Go pictures vs Neutral Go pictures in right dorsal cingulate cortex and bilateral DLPFC. Regarding the inhibitory control during neutral pictures PGs activated more bilateral DLPFC and right ACC. HCs showed more bilateral DLPFC and right ACC activity than PGs

during Gamble No-Go trials compared to Neutral No-Go trials. Moreover HCs showed increased activation in bilateral DLPFC and left ventral striatum compared to PGs during positive inhibition and more activation in right DLPFC and left ACC during Negative No-Go compared to Neutral No-Go trials. This study shows that gambling-related and other affective stimuli are more salient for PGs than for HCs. Also, compared to the control group, PGs rely on compensatory brain activity to achieve similar performance during neutral response inhibition. A gambling-related or positive context, however, appears to facilitate response inhibition in PGs as indicated by lower brain activity and fewer behavioural errors.

In our study we used a similar procedure of the research described above. We designed a Go-NoGo task including affective pictures to investigate salience attribution and inhibitory control in a group of PGs starting a treatment. The choice of this task is referred to the proposal of retesting the subjects at the end of the therapy to highlight the brain changes associated with the treatment. In details, our next aim will be the evaluation of two different non-pharmacologic therapies for pathological gambling, Functional Therapy (FT) and Trancranial Magnetic Stimulation (TMS). Hovewer in this thesis we are presenting only the preliminary results.

4.3 METHODS

4.3.1 Subjects

Eleven right-handed PGs and three HCs, ranging 26-53 participated in the study. PGs were recruited from an Italian addiction center where received a treatment while Hcs were recruited through advertisements. Because most treatment seeking PGs are men, only male participants were included in the study. Exclusion criteria for both groups were: lifetime diagnosis of schizophrenia or psychotic episodes; diagnosis of manic disorder, obsessive compulsive disorder, alcohol use disorders, substance dependent disorder or post-traumatic stress disorder; treatment for mental disorders other than pathological gambling in the past 12 months; use of psychotropic medication; difficulty reading Italian; age under 18 years; history or current treatment for neurological disorders,

major internal disorders, brain trauma, or exposure to neurotoxic factors. In addition, HCs were excluded if they gambled more than twice a year.

4.3.2 Procedure

The study was introduced to the participants as an investigation on behavioural and personality traits as well as the brain areas involved in gambling, and they were asked to answer self-report questionnaires and undergoing to a fMRI anonymously. All measures were administered under respect of privacy. A signed informed consent was obtained from each subject after the procedures were fully explained. To evaluate the inhibitory control in the context of neutral and affective stimuli we designed a Go-NoGo task based on van Holst et al. (2012). This task consisted of four different blocks containing positive, neutral, negative and gambling-related pictures. The positive, negative, and neutral pictures were selected from the International Affective Picture System (IAPS) (IAPS: Lang et al., 2008) based on their valence and arousal scores. Gambling related pictures were taken from casino scenes, slot-machines and scratch cards. All the pictures were matched on visual properties such as brightness and complexity. Before each block started, an instruction appeared on the screen for 15 seconds, instructing participants to press a button when a certain type of stimulus was shown (Go trials) and to inhibit pressing the button when a neutral stimulus type was shown (No-Go trials). Each block consisted of 35 pictures, which were shown 4 times, presented in rapid succession for 800 ms each. To evoke an automated response, 100 Go trials and 40 No-Go trials were randomly presented. No-Go trials never occurred more than twice in a row. In the gambling block, for example, the instruction was to respond as accurately and fast as possible to gambling-related pictures, and not to respond to neutral pictures (see Figure 1). Because all pictures were neutral in the neutral block, participants were instructed to respond to all neutral pictures, but not to respond when a vehicle was shown in the picture Behavioural outcomes of interest included percentage of impulsive errors and mean reaction times in the different blocks.

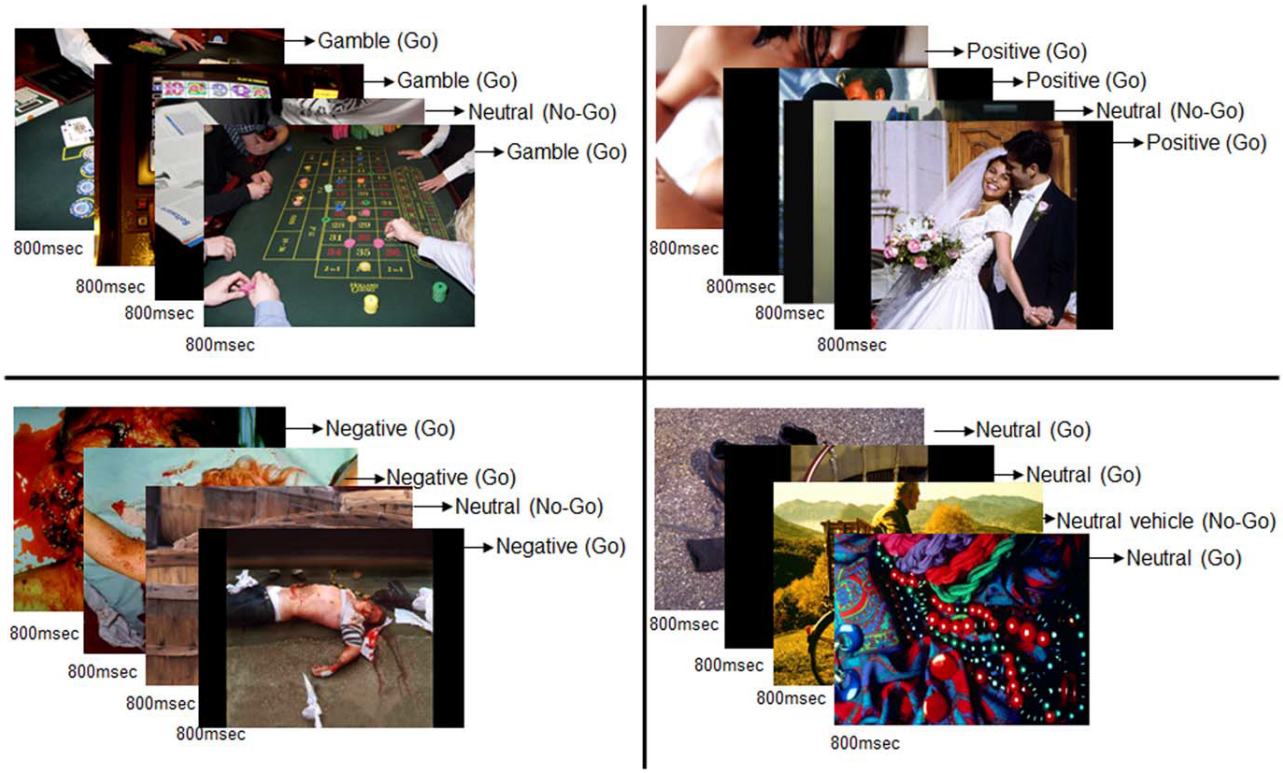

Figure 1. Example of the four blocks of the Go-NoGo task.

4.4 MEASURES

4.4.1 Socio-Demographic Variables

A socio-demographic questionnaire was used to ask participants about their age, marital status, occupation, habitual residence, and socio-economic status.

4.4.2 Gambling Behaviour Assessment

All subjects completed the South Oaks Gambling Screen (SOGS). The SOGS is a 20 items questionnaire that measures gambling behaviour through questions on participant's history of gambling, the frequency at which the person engages in these behaviours, and obstacles that gambling may have posed in the participant's life. The total score on the SOGS ranges from 0 to 20 (scores from 5 indicates probable pathological gambling) (Lesieur & Blume 1987).

4.4.3 Personality disorders and clinical syndromes

To evaluate personality disorders and clinical syndromes we used the third version of Millon Clinical Multiaxial Inventory (MCMI-III) (Millon, 1994). MCMI-III is a 175-item true/false self-

report instrument that assesses Axis I and Axis II psychopathology. Based on Theodore Millon Evolutionary Theory of personality and psychopathology, the MCMI-III identifies 14 personality disorder scales and 10 clinical syndrome scales. The MCMI-III raw scores are reported as weighted base rate (BR) scores. Previous studies have shown good internal consistency (α = .66–.90) and stability (test-retest r = .84–.96) for the MCMI-III scales (Zennaro, Ferracuti, Lang & Sanavio, 2008).

4.4. Impulsivity

To evaluate impulsiveness we used the Barratt Impulsiveness Scale, 11th version (BIS-11) (Barratt, 1985). The BIS-11 is a self-report questionnaire, which contains 30 questions that need to be scored on a scale from 1 to 4 (1=rarely/never; 2=occasionally; 3=often; 4=almost always/always). Factor analysis includes 6 first order factors (attention, motor impulsiveness, self-control, cognitive complexity, perseverance and cognitive instability) and 3 second order factors (attentional impulsiveness, motor impulsiveness and non-planning impulsiveness). The BIS-11 total score indicates the level of impulsiveness. The higher the BIS-11 total score, the higher the impulsiveness level is. The questionnaire contains statements that indicate impulsive behaviour ('I do things without thinking') and statements that indicate non-impulsive behaviour ('I am self-controlled'). The BIS-11 is the most frequently used self-report measure of impulsivity.

4.4.5 Cognitive Distortions

To evaluate the cognitive distorsions we used the Italian version of the Gambling Attitudes and Beliefs Survey (GABS) (Breen e Zuckerman, 1999). The GABS is a self-report questionnaire, which contains 35 questions related to possible cognitive distorsions or different kind of thinking.

4.4.6 fMRI analysis

Imaging data were obtained from the Radiology Unit of the Policlinico "P. Giaccone" of Palermo and data were analysed at the Academic Medical Center, Department of Psychiatry of the

University of Amsterdam under the supervision of Prof. A.E. Goudriaan and of Dott. R.J. van Holst. The MRI scanner we used was a Signa HDxt General Electric Medical Systems – Milwaukee, WI a 1,5 T. fMRI analysis was performed through the Statistical Parametric Mapping - eight version (SPM-8) (Statistical Parametric Mapping; Wellcome Trust Centre for Neuroimaging, London, UK). SPM-8 is an academic software toolkit for the analysis of functional imaging data developed by Friston et al., at the University College of London. It is the most used software to analyze fMRI data and it requires a Matlab interface. Images were preprocessed, manually reoriented, slice-timed, realigned and unwarped. Then, images were normalized to MNI (Montral Neurological Institute). Next, and analyzed through a *first level* (intra-subjects) and a *second level* (inter-subjects) analysis. All fMRI data were analyzed within the context of the General Linear Model with an uncorrected threeshold set at $p<0.001$, carrying out a "*whole-brain*" analysis.

To test the effect of salience attribution we investigated the contrasts: "Gamble Go vs Neutral Go", "Positive Go vs Neutral Go", and "Negative Go vs Neutral Go". Response inhibition was investigated with the contrast: "Neutral NoGo vs Neutral Go". Finally the response inhibition in the context of affective pictures was examined with the contrasts: "Gamble NoGo vs Neutral NoGo", "Positive NoGo vs Neutral NoGo", and "Negative NoGo vs Neutral NoGo".

4.5 STATISTICAL ANALYSIS

Individual mean reaction were based only on correct responses. Statistical analysis was conducted on SPSS for Windows 20.0. One-way analysis of variance (ANOVA) was used to analyse sociodemografic data. Reaction times and non-normally distributed data were analyzed using Mann- Whitney U-test for the comparison between groups. All analysis were performed two-tailed with an alpha of 0.05.

4.6 RESULTS

4.6.1 Sociodemografic and psicodiagnostic data

Data analysis revealed no significant difference between groups on age ($F = 4.539$, $p=.055$)

and education level (F = 2.930, p=.113). As expected PGs showed a higher comorbidity of psychiatric disorders, compared to HCs. The percentage of PGs diagnosed as a personality disorder was 63.6% and the most frequent was the negativistic personality disorder (54.5%). More than half of PGs (54.5%) was diagnosed as an Axis I disorders and the more prevalent were anxiety (36.3%) and dysthymia (18.18%). In the control group no one showed scores useful to receive an Axis I or Axis II diagnosis. Significant differences between groups were found in impulsivity (p=.005) but not regarding the presence of cognitive distorsions (p=.088).

4.6.2 Behavioural performance on the Go-NoGo task

No significant differences between groups were found on reaction times (Table 2) and percentage of errors during the different blocks (Table 3). However, PGs responded slower than HCs and made fewer impulsive errors during the gambling block (data not published), congruent with van Holst et al. study described above.

Table 2. Reaction times during the different Go-NoGo blocks

REACTION TIMES	TEST Mann-Whitney U
TOT	p=.291
POSITIVE BLOCK	p=.555
NEUTRAL BLOCK	p=.126
GAMBLING BLOCK	p=.555
NEGATIVE BLOCK	p=.126

Table 3. Percentage of impulsive errors during the different Go-NoGo blocks

IMPULSIVE ERRORS	TEST Mann-Whitney U
POSITIVE NOGO	p=.769
NEUTRAL NOGO	p=.291
GAMBLING NOGO	p=.225
NEGATIVE NOGO	p=.769

4.6.3. fMRI results

Salience attribution

To test differences in salience attribution towards affective stimuli between groups we compared brain activation during the contrasts: “Gambling Go vs Neutral Go”, “Positive Go vs Neutral Go” e “Negative Go vs Neutral Go”.

Group interaction Gambling Go versus Neutral Go

PGs showed increased activity in associative visual cortex (Brodmann area 19) (peak voxel: x, y, z = 26, 58, -6, T = 4.56, kE=17) (Figure 2). HCs showed no areas that were more active than in PGs.

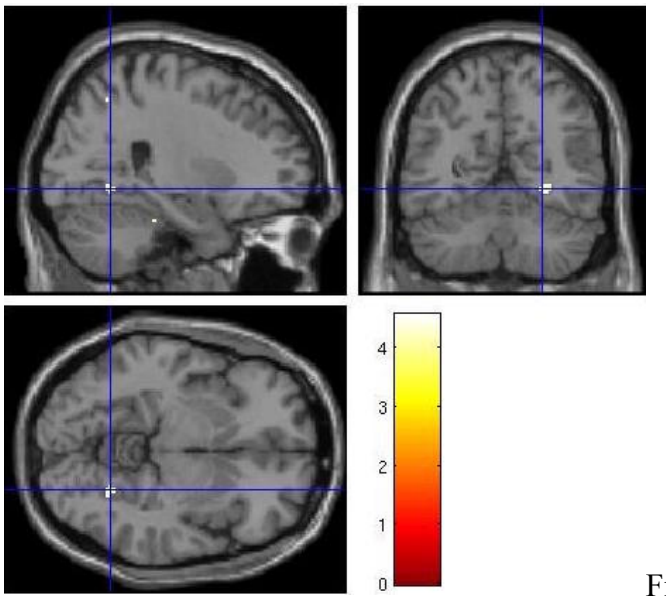

Figure 2

Group interaction Positive Go versus Neutral Go

PGs showed enhanced activity in right inferior frontal gyrus (peak voxel: x, y, z = 48, 36, 0, T = 5.35 kE=9) (Figure 3) and in visual cortex (peak voxel: x, y, z = 26, -70, 12, T = 5.21, kE=8) (Figure 4). HCs showed no areas that were more activated than in PGs.

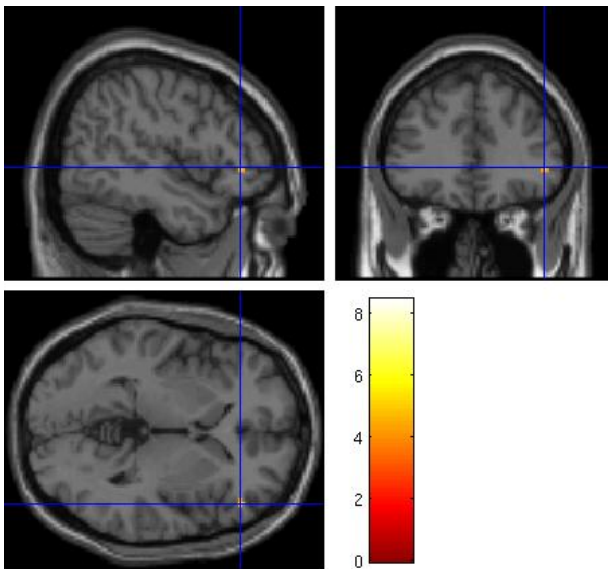

Figure 3

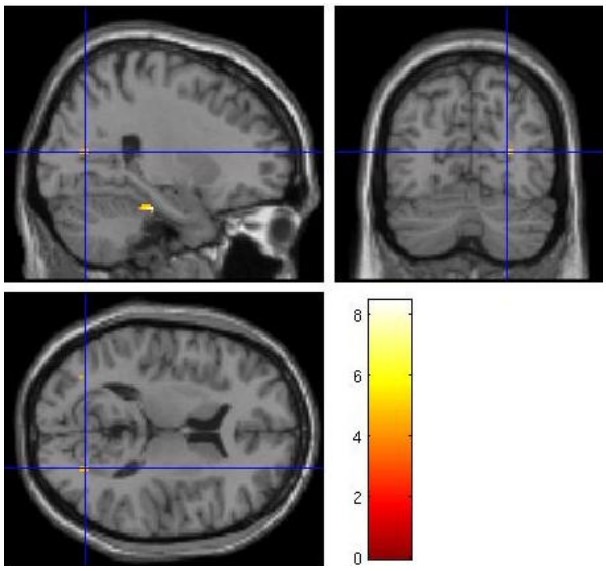

Figure 4

Group interaction Negative Go versus Neutral Go

No significant differences between groups regarding this contrast were found.

Neutral response inhibition

To test the differences between groups on neutral response inhibition we analyzed the BOLD response during the contrast "Neutral Go vs Neutral NoGo".

Group interaction Neutral Go versus Neutral NoGo

PGs showed no increased activity compared to HCs on this contrast. Otherwise HCs revealed more activity in medial frontal gyrus (peak voxel: x, y, z = -6, 56, 22, T = 5.08, kE=9) (Figure 5) and ACC (peak voxel: x, y, z = -14, 32, 28, T = 5.06, kE=23) (Figure 6).

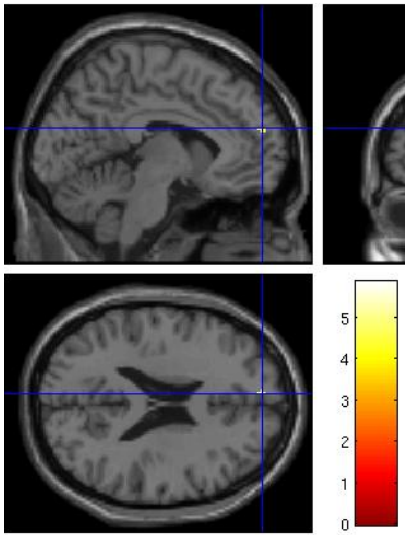

Figure 5

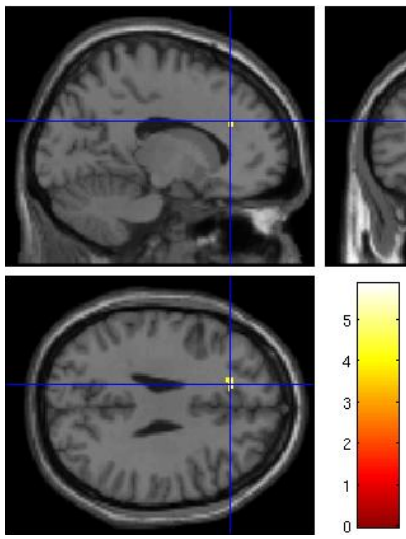

Figure 6

Response inhibition during affective blocks

The effect of affective stimuli on response inhibition was evaluated by analysing the BOLD response during these contrasts: "Gambling NoGo vs Neutral NoGo", "Positive NoGo vs Neutral NoGo" e "Negative NoGo vs Neutral NoGo".

Group interaction Gambling NoGo versus Neutral NoGo

No significant differences between groups regarding this contrast were found..

Group interaction Positive NoGo versus Neutral NoGo

PGs showed enhanced brain activity in left medial frontal gyrus (peak voxel: x, y, z = 38, 50, -10, T = 5.99, kE=9) (Figure 7) and cingulate gyrus (peak voxel: x, y, z = -6, 18, 46, T = 5.82, kE=34) (Figure 8).

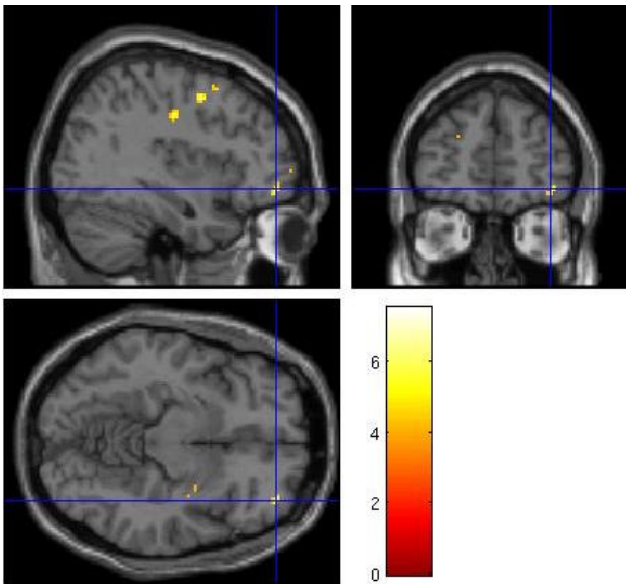

Figure 7

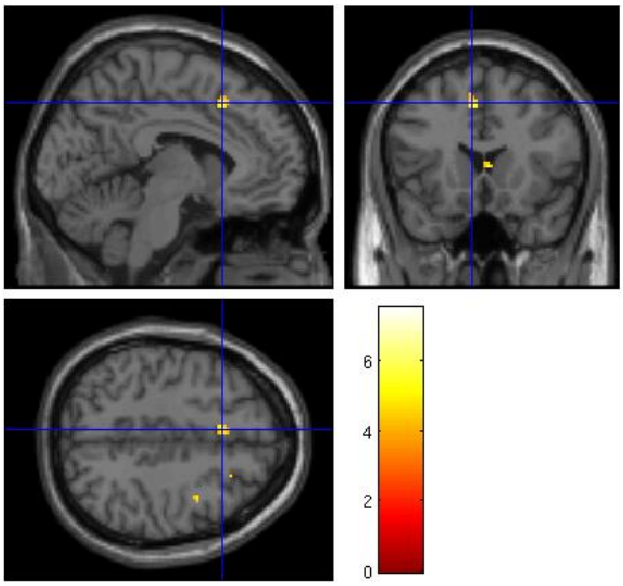

Figure 8

Group interaction Negative NoGo versus Neutral NoGo

No significant differences between groups regarding this contrast were found..

4.7 DISCUSSION

In this study we used a Go-NoGo task, based on van Holst et al. (2012), to investigate in PGs, compared to HCs, the brain activity related to salience attribution and response inhibition on neutral, gambling-related and affective stimuli. Unfortunately the paucity of subjects recruited and the differences between groups do not allow to make strong inferences. Hovewer, we can make some useful consideration.

Large amount of comorbidities in pathological gambling

In this study was highlighted a strong presence of comorbidities in PGs compared to HCs, confirming previous research (Maniaci et al., 2015; Odlaug et al., 2013; Petry et al., 2005). In particular we found a remarkable presence of anxiety, dysthymia and personality disorders. Furthermore in the clinical group significant more impulsivity levels were found, confirming an important role for impulse dyscontrol in pathological gambling (Castellani & Rugle, 1995; Marazziti et al., 2014).

No differences in behavioural performance on Go-NoGo task

No significant differences between groups are revealed regarding the behavioural performance on the Go-NoGo task, concerning reaction times and percentage of impulsive errors. However, the direction of the differences highlighted appears congruent with van Holst et al. study. Indeed despite the lack of a statistical significance between groups, PGs tend to answer slower than control committing less impulsive errors during gambling-related block. It could be possible to obtain a statistical significance by enlarging the number of subjects recruited.

Pathological gamblers show enhanced salience to gambling and positive stimuli

Congruent with our hypothesis and with van Holst et al. study, we found that watching gambling-related pictures PGsshowed an enhanced salience attribution underlined by the activation of the associative visual cortex, suggesting that these pictures increased the visual attention and the motivation to produce a better performance in PGs. Furthermore, watching positive pictures, PGs showed enhanced activity in right inferior frontal gyrus and in visual cortex, indicating again an enhanced salience attribution. These data are congruent with previous studies on pathological gambling (Goudriaan et al., 2010; Crockford et al., 2005) and alcohol addiction (Heinz et al., 2007).

During neutral inhibition, HCs recruit additional brain regions to perform similar to PGs

Contrary to van Holst et al. results but congruent with their hypothesis we found in PGs a diminished activity in the medial frontal gyrus and in the anterior cingulate cortex during the

response inhibition in the neutral block. This data appears as a confirm of the I-RISA model suggesting an influence of pathological gambling on prefrontal cortex activity.

During positive response inhibition PGs recruit additional brain regions to perform similar to HCs

Regarding the response inhibition during affective block, differences between groups were found in the Positive NoGo versus Neutral NoGo stimuli. During this contrast PGs showed increased activity in the left middle frontal gyrus and in the right cingulate gyrus, suggesting that PGs need to recruit additional brain region to perform similar to HCs.

Strengths, limitations and suggestions for future research

The present study has some limitations. First, the small number of subjects recruited does not allow to generalize the results. Furthermore, groups differ regarding the sample size. Strengths include the use of a paradigm that probes motivational as well as cognitive systems simultaneously, providing the chance to study their interaction in PGs. Moreover these data are relevant because they confirm and highlight the opportunity to investigate how salience attribution and inhibitory control are modified through a treatment. In this regard, many studies showed the importance to find evidence-based therapies for pathological gambling (Yip & Potenza, 2014) and our study represents an interesting start point to study how the PGs brain changes after a treatment, as we mean to do.

4.8 CONCLUSIONS

This study shows that gambling-related and positive pictures are more salient for PGs compared to HCs. Also, PGs showed decreased prefrontal activity during neutral inhibition and more during positive inhibition. Hovewer behavioural performance on the Go-NoGo task was not significantly different between groups.

Researchers involved in the study: Maniaci G., Piccoli T., Picone F., van Holst R.J., Goudriaan A.E., Lipari A., Scardina S., Gagliardo C., Bolloni C., & Cannizzaro C.

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GENERAL DISCUSSION

In this thesis we presented a research concerning the assessment of gambling disorder, organized in four different but intercorrelated studies. Remaining in the field of the clinical neuroscience we started from a psychodiagnostic point of view, passed from a neurobiological approach, concluding with a neurofunctional assessment. Pathological gambling is an heterogeneous disorder and it requires the adoptation of a multidimensional diagnostic approach to better understand this disorder from different angles (Caretti and La Barbera, 2010).

The **first part** of this thesis was oriented to the evaluation of the comorbidity in pathological gambling. We used a psychodiagnostic approach to evaluate 70 pathological gamblers (PGs), compared to 70 healthy controls (HCs), highlighting a remarkable presence of Axis I and Axis II disorders, confirming previous studies (Kerber et al., 2008; Odlaug et al., 2012; Petry et al., 2005).

The **second part** showed the relevant role of alexithymia and anger expression in pathological gambling. We evaluated 100 PGs, compared to 100 HCs, using psychological tests showing that anger is strongly related to gambling behaviour after controlling for alexithymia.

The **third part** has oriented the assessment process through the neurohormonal and neurovegetative point of view. In particular the study was aimed at investigating the effect of the Trier Social Stress Test on cortisol and on interbeat interval in relation to impulsivity measure in a sample of male PGs, compared to HCs. The results showed that gambling disorder appears related to HPA axis activity and particularly to a lower availability of cortisol in gamblers with a longer duration of the disorder. Moreover the association among the physiological stress response and impulsivity appears to be relevant in the understanding of several facets of gambling disorder.

Finally the **fourth part** of the thesis investigated the salience attribution and the inhibitory control in PGs tested in a Go-NoGo task during a functional magnetic resonance sesssion, thus

orienting the assessment on the neurofunctional side. Results showed an enhanced salience attribution on gambling-related and positive pictures. Furthermore PGs showed diminished prefrontal activity during neutral response inhibition and more prefrontal activity during positive response inhibition, thus partially confirming the Impaired Response Inhibition Attribution model.

These preliminary data, taking into account the limitations of the study, are relevant because allow us to move our efforts to another step of the assessment process of gambling disorder, namely the evaluation of the brain changes in PGs after a treatment. In particular we are working on the assessment of the efficacy of two different non-pharmacologic treatments for PGs, Functional Therapy (FT) and Transcranial Magnetic Stimulation (TMS). Currently we completed the treatment of three PGs through the FT and 2 through the TMS. However the number of subjects recruited is too small to allow us to make strong considerations.

I would like to conclude my thesis providing a personal comment, as a result of the work of these years. It is well-known that, both in psychology and medicine, clinical and research activity are strongly interrelated fields. I think that this is all the more true concerning the study of addictions area, where preclinical and clinical studies are fundamental for the discovering of new treatments and clinical activity it is equally essential to the development of new aims for new studies.

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