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Network strumentali e funzionali del GAP: *correlati cognitivi e di neuroimaging*

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GAMBLING DISORDER

- Fenomeni di *tolleranza, dipendenza*, c*raving*
- Ripetuti tentativi di smettere di giocare
- Interferenza in molte aree funzionali della vita
- Continua occupazione nel comportamento d'abuso nonostante le conseguenze avverse
- Progressiva riduzione del controllo sul comportamento d'abuso
- Impegno compulsivo nel comportamento d'abuso

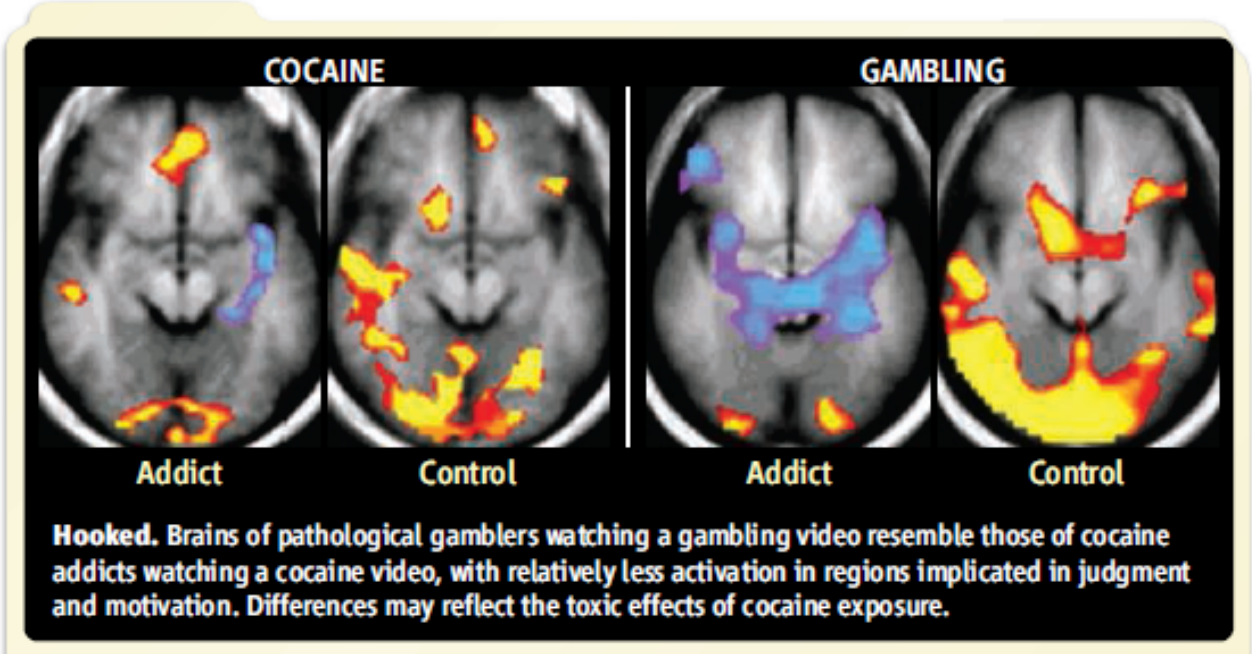
DSM 5 Gambling Disorder

↓

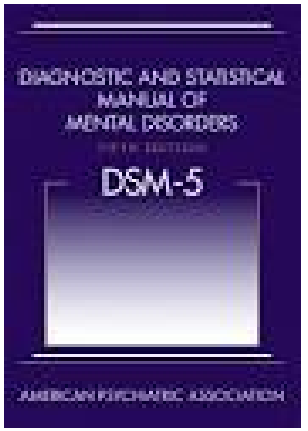
Substance-Related and Addictive Disorders

Behavioral addictions: DSM-5

- The DSM-5 included GD in the diagnostic category of ‘Substance-related and Addictive Disorders’ (APA, 2013).



Hooked. Brains of pathological gamblers watching a gambling video resemble those of cocaine addicts watching a cocaine video, with relatively less activation in regions implicated in judgment and motivation. Differences may reflect the toxic effects of cocaine exposure.



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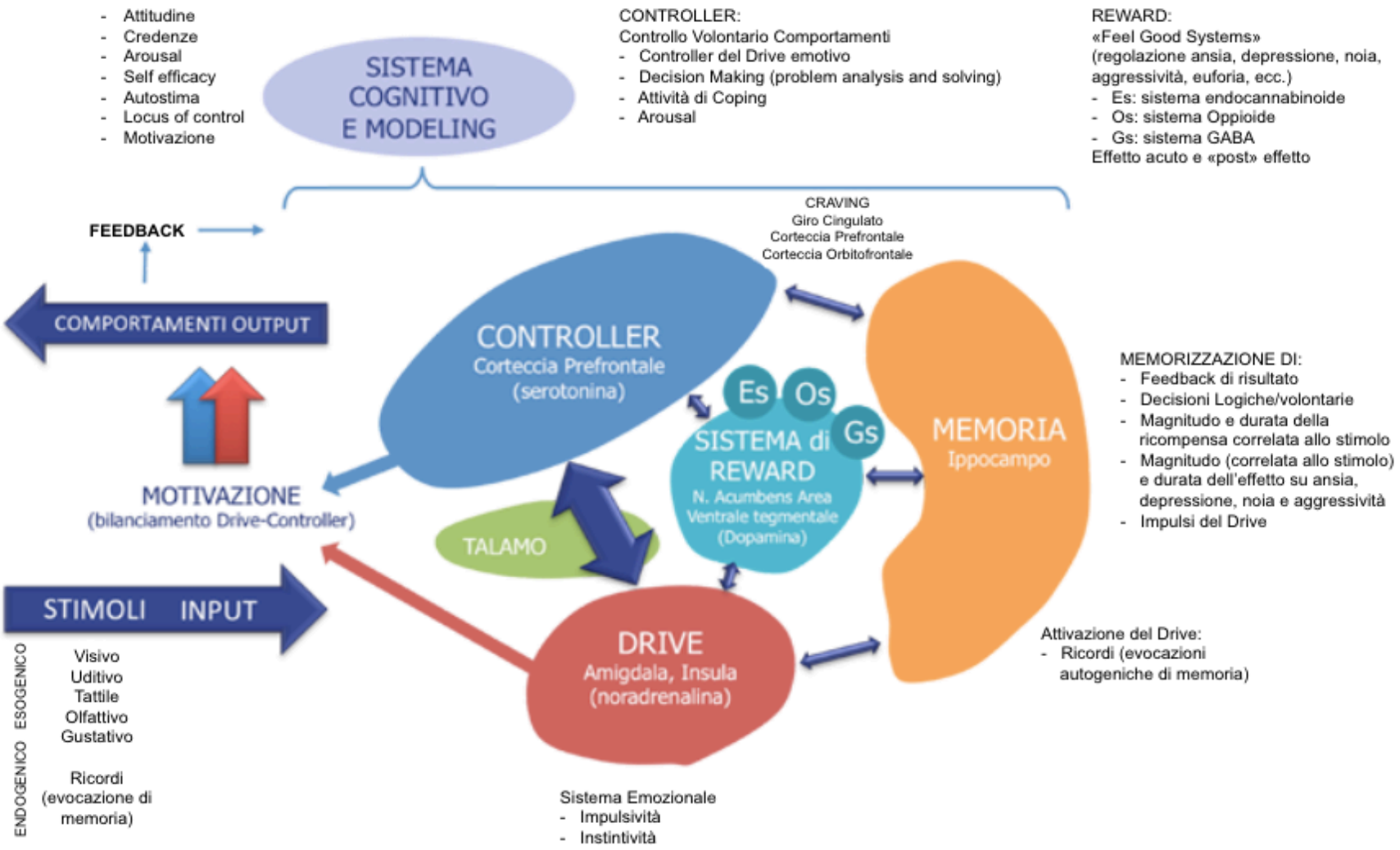
Neurotransmitter	PG results	SUD results: similarities/differences with PG
Dopamine	*Limited impulsivity findings*: In PD, agonist use associated with increased delay discounting in those with ICD.	Activity proposed to contribute to delay discounting in SUDs.
	Limited compulsivity findings: Equivocal results with agonists in animal models.	Activity proposed to contribute to compulsivity in SUDs.
	Elevated release during gambling task performance in some with PG (with and without PD), but also individual differences.	Substance use typically associated with release, but also individual differences.
	Equivocal findings with antagonist use	Equivocal findings with antagonist use
Serotonin	Low levels of 5-HIAA in PG	Low levels of 5-HIAA in SUDs
	mCPP associated with subjective "high" in PG	mCPP associated with subjective "high" in SUDs
	Blunted growth hormone response to sumatriptan	Blunted growth hormone response to sumatriptan
	Evidence suggests role for 5HT1B receptor function	Evidence suggests role for 5HT1B receptor function
	Mixed results in efficacy of SSRIs for PG	Mixed results in efficacy of SSRIs for SUDs
Opioids	Evidence of involvement in gambling behavior and urges. Strong evidence for treatment efficacy of antagonists.	Evidence of involvement in substance use behavior and urges. Strong evidence for treatment efficacy of antagonists, particularly for alcohol and opioid dependence.
Glutamate	Preliminary evidence for efficacy of medications that alter transmission, with possible involvement in impulsive and compulsive behaviors.	Preliminary evidence for efficacy of medications that alter transmission, with possible involvement in impulsive and compulsive behaviors.
Norepinephrine	Elevated activity in PG, particularly during gambling.	Elevated during use of some substances, particularly stimulants like cocaine.

5-HIAA 5-hydroxyindoleacetic acid, *PD* Parkinson's disease, *ICD* impulse control disorder, *mCPP* meta-chlorophenylpiperazine, *SSRI* selective serotonin reuptake inhibitor


- Attitudine
- Credenze
- Arousal
- Self efficacy
- Autostima
- Locus of control
- Motivazione
SISTEMA COGNITIVO E MODELING
CONTROLLER:
Controllo Volontario Comportamenti
- Controller del Drive emotivo
- Decision Making (problem analysis and solving)
- Attività di Coping
- Arousal
REWARD:
«Feel Good Systems»
(regolazione ansia, depressione, noia, aggressività, euforia, ecc.)
- Es: sistema endocannabinoide
- Os: sistema Oppioide
- Gs: sistema GABA
Effetto acuto e «post» effetto
FEEDBACK
CRAVING
Giro Cingulato
Corteccia Prefrontale
Corteccia Orbitofrontale
COMPORTAMENTI OUTPUT
CONTROLLER
Corteccia Prefrontale
(serotonina)
Es
Os
Gs
SISTEMA di REWARD
N. Acumbens Area Ventrale tegmentale
(Dopamina)
MEMORIA
Ippocampo
MOTIVAZIONE
(bilanciamento Drive-Controller)
TALAMO
MEMORIZZAZIONE DI:
- Feedback di risultato
- Decisioni Logiche/volontarie
- Magnitudo e durata della ricompensa correlata allo stimolo
- Magnitudo (correlata allo stimolo) e durata dell'effetto su ansia, depressione, noia e aggressività
- Impulsi del Drive
STIMOLI INPUT
ENDOGENICO ESOGENICO
Visivo
Uditivo
Tattile
Olfattivo
Gustativo
Ricordi
(evocazione di memoria)
DRIVE
Amigdala, Insula
(noradrenalina)
Attivazione del Drive:
- Ricordi (evocazioni autogeniche di memoria)
Sistema Emozionale
- Impulsività
- Instintività

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Common neurobiological features SUD - GD

Brain region/structure	PG results	SUD: similarities/differences with PG
Frontal cortical regions	*Response impulsivity tasks*: PG/problem gamblers demonstrate less activity than do controls.	SUD/substance users also demonstrate less activity than controls.
	Compulsivity tasks: PG/problem gamblers demonstrate less activity than do controls. Lesion studies suggest vmPFC and dlPFC are important for task performance.	Smokers also demonstrate less activity than do controls.
	Risk/reward tasks: PG/problem gamblers demonstrate less activity than do controls. In PD, less activity among those with ICDs, greater activity in those without ICDs.	Most findings also suggest less activity in SUD groups than in controls.
Striatum	*Baseline*: Limited results have been variable regarding D2-like receptor availability in PG. Limited evidence suggests dorsal hyperactivity.	Reduced D2-like receptor availability in SUD/ substance users. Dorsal hyperactivity in SUD also.
	Impulsivity and compulsivity tasks: Limited findings suggest no differences between PG and controls.	Limited findings suggest no differences between substance users and controls.
	Risk/reward tasks: In PG, less ventral activity than in controls and association with impulsivity. Some evidence of elevated dorsal activity in PG. Findings more variable in PD studies.	Some similar findings of diminished ventral activity in SUD/substance users with similar associations with impulsivity (particularly in alcoholism), but opposing findings of elevated activity as well.
Anterior cingulate cortex (ACC)	Findings that "loss chasing" is associated with elevated activity in healthy adults suggest a role in gambling.	Associated with risky decision-making in SUDs.
Insula	Activated by healthy adults and occasional gamblers during gambling tasks and by healthy adults in response to "near misses" during gambling tasks.	Activated in response to reward by substance users.
White matter integrity	PG reduced FA values in the corpus callosum.	Poor white matter integrity observed diffusely both in heavy substance users and in SUDs

PD Parkinson's disease, *ICD* impulse control disorder, *FA* fractional anisotropy

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Reduced genual corpus callosal white matter integrity in pathological gambling and its relationship to alcohol abuse or dependence

Table II. Results of between group comparisons of CC diffusion parameters.

	PGs versus matched HCs				
	HCs (n = 19)	PGs (n = 19)			
ROIs	Mean FA values ± SD		F	P	df
L Genu	0.587 ± 0.060	0.520 ± 0.073	**9.446**	**0.004**	1
R Genu	0.587 ± 0.063	0.519 ± 0.078	**8.585**	**0.006**	1
L Body	0.557 ± 0.050	0.521 ± 0.057	**4.326**	**0.045**	1
R Body	0.536 ± 0.047	0.506 ± 0.058	3.098	0.087	1
L Splenium	0.620 ± 0.047	0.610 ± 0.060	0.328	0.570	1
R Splenium	0.609 ± 0.050	0.506 ± 0.058	0.242	0.626	1
	Mean perpendicular ± SD				
L Genu	0.512 ± 0.075	0.589 ± 0.113	**6.186**	**0.018**	1
R Genu	0.508 ± 0.077	0.580 ± 0.110	**5.483**	**0.025**	1
L Body	0.534 ± 0.063	0.575 ± 0.080	3.080	0.088	1
R Body	0.561 ± 0.064	0.591 ± 0.086	1.498	0.229	1
L Splenium	0.510 ± 0.086	0.523 ± 0.120	0.140	0.710	1
R Splenium	0.542 ± 0.105	0.531 ± 0.089	0.124	0.727	1

- Findings of decreased FA values in the genu of the CC in PG subjects suggest that, like with other disorders of behavioral dyscontrol, white matter microstructural abnormalities contribute to the pathophysiology of PG.

- These differences appear particularly relevant to individuals with remitted AA/AD.

Yip et al., 2011. The World Journal of Biological Psychiatry

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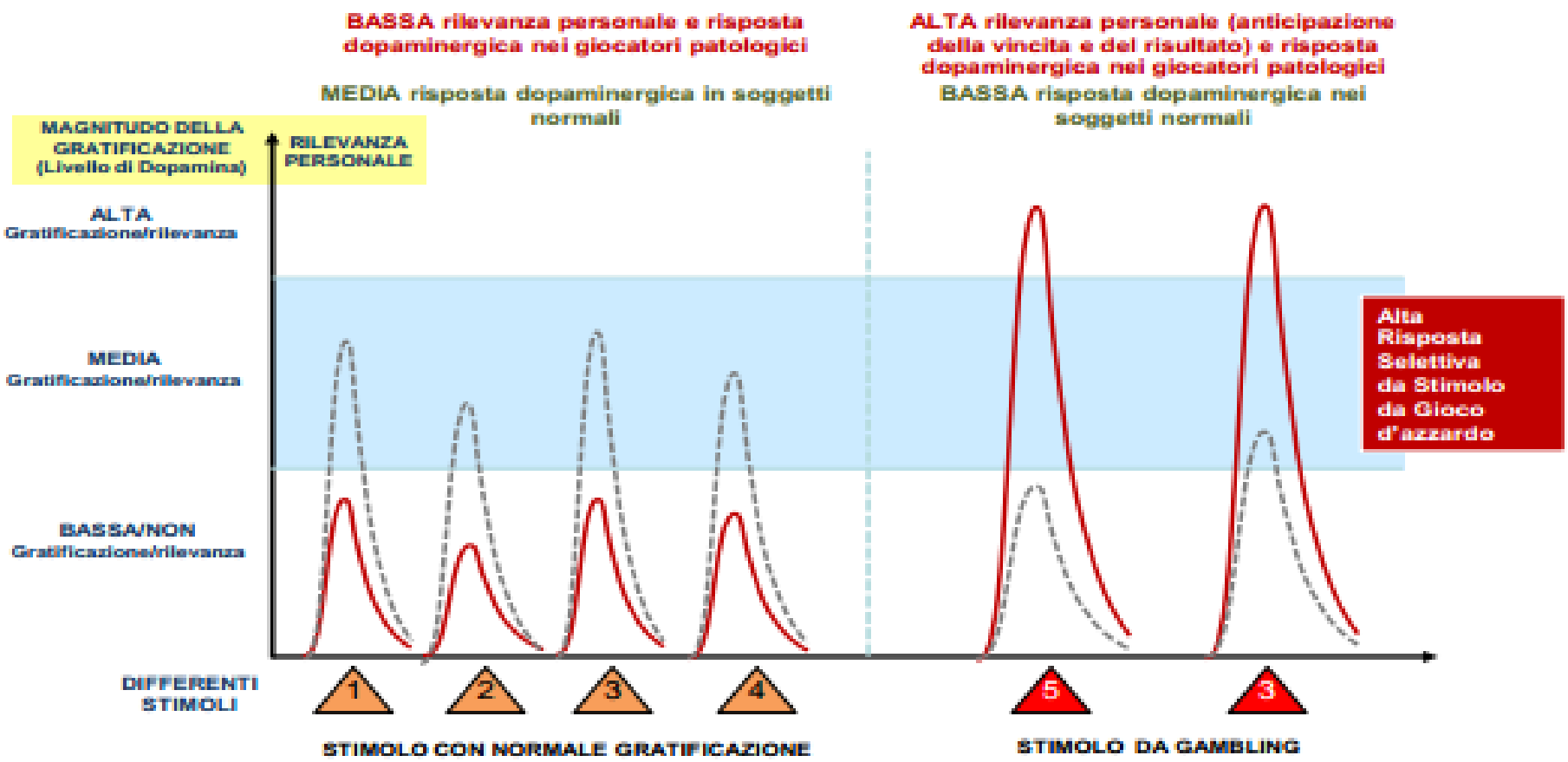
Gambling disorder e sistema del *reward*



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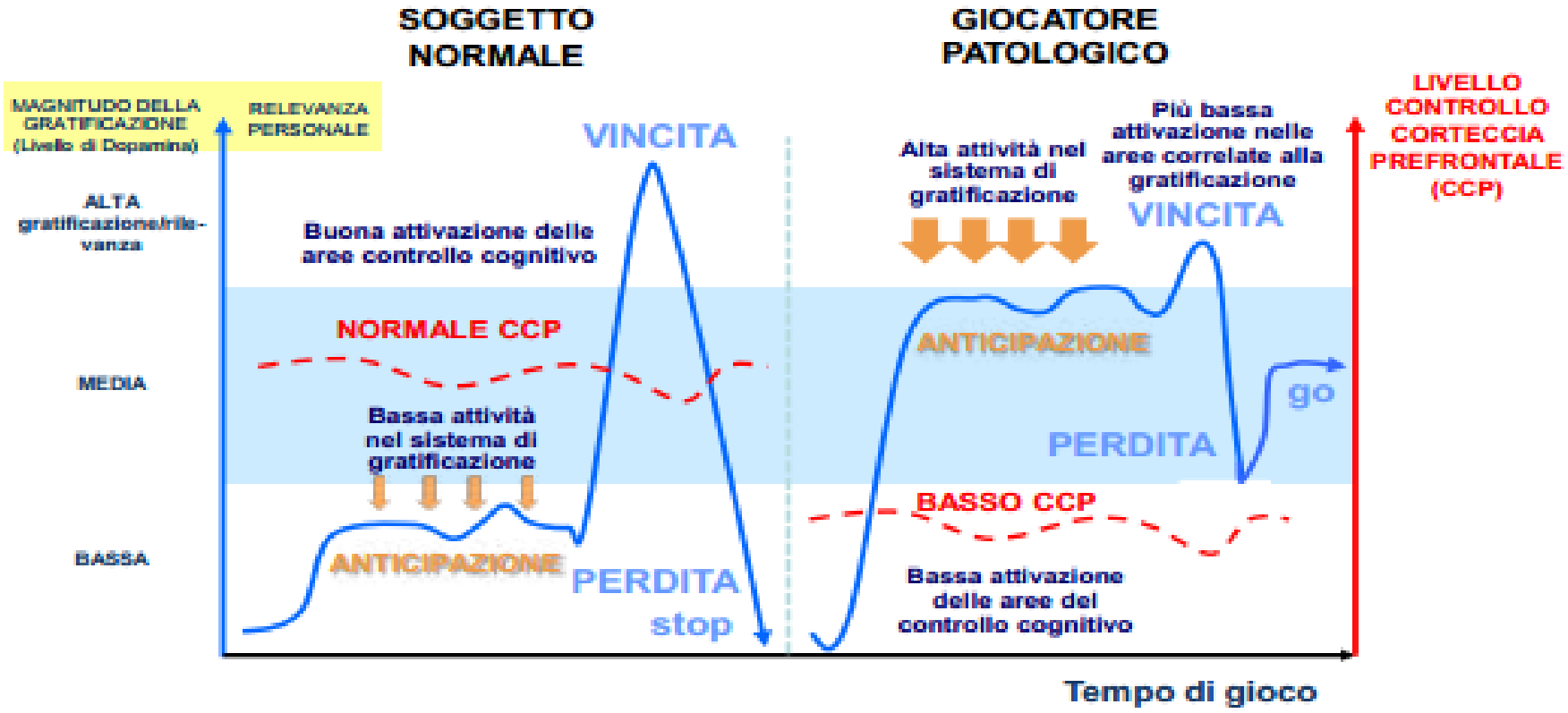
Gambling disorder e sistema del *reward*



Soggetti con GAP : maggior gratificazione nell'anticipazione, minor gratificazione postvincita, basso CCP
Soggetti normali: minor gratificazione nell'anticipazione, maggior gratificazione postvincita, normale CCP

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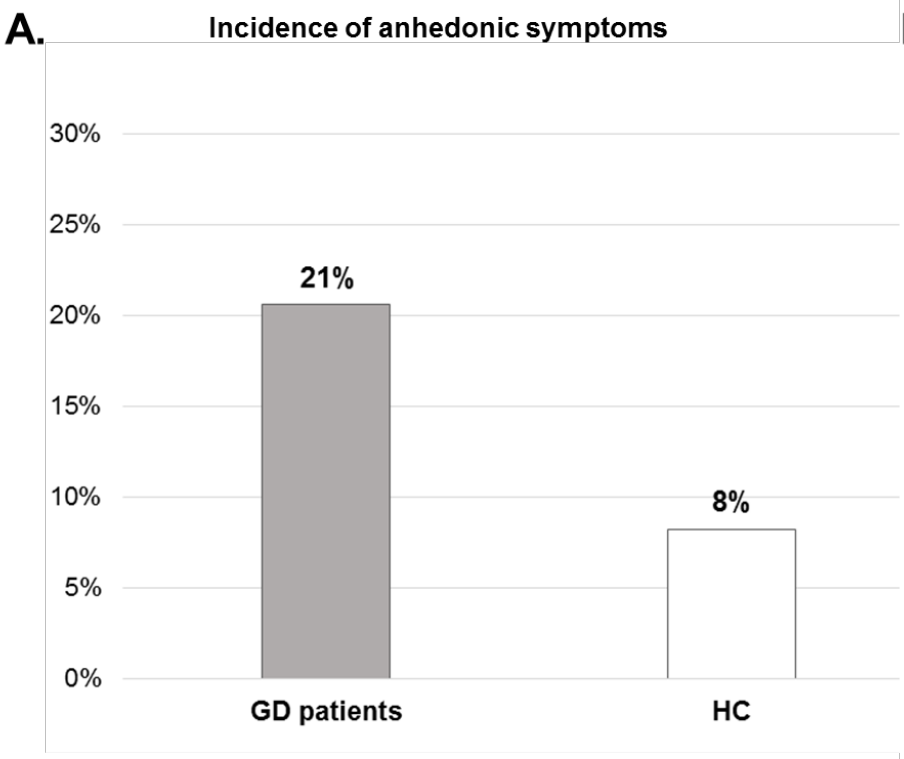
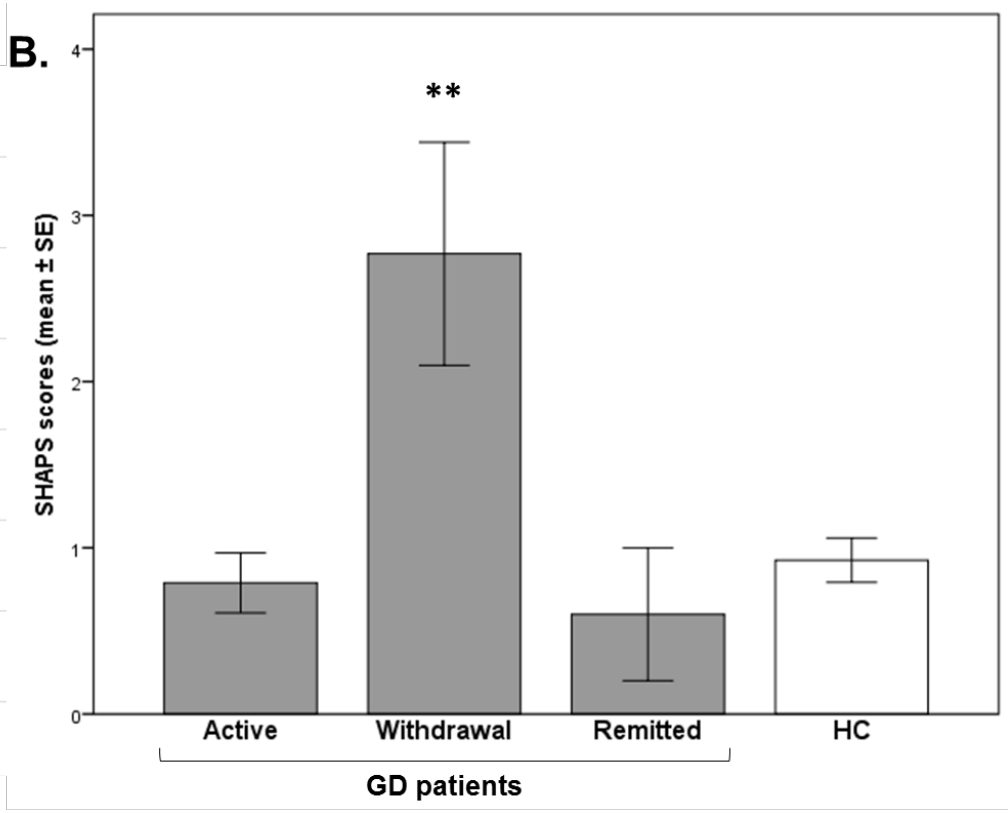
Hedonic tone and protracted-withdrawal in GD

- We firstly investigated the impact of hedonic tone dysfunction in GD across different phases of the disorder, relating this measures to preliminary findings on DAT availability assessed using ^{123}I-FP-CIT SPECT
- **69 subjects** meeting DSM-5 diagnostic criteria for GD, were divided into **three groups** according to abstinence/remission criteria:
  - *active pathological gamblers*
  - *withdrawal group (1-6 months abstinence)*
  - *full remitted*

Pettorruso et al., *Addiction Biol, 2018*

Hedonic tone and protracted-withdrawal





- In comparison with HC, elevated levels of anhedonic symptoms were observed in GD patients (21% vs 8%)
- GD patients experienced low hedonic tone during gambling withdrawal

Pettorruso et al., *Addiction Biol, 2018*

ORIGINAL ARTICLE

WILEY Addiction Biology SSA

Striatal presynaptic dopaminergic dysfunction in gambling disorder: A ^{123}I-FP-CIT SPECT study

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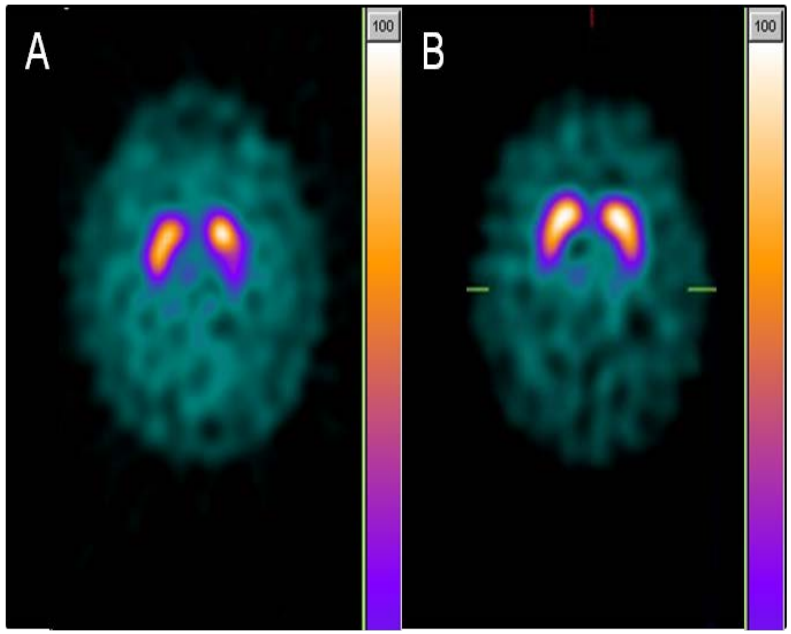

Abstract

Although the involvement of dopamine in gambling disorder (GD) has long been hypothesized, its precise role remains unclear. The action of dopamine in the synapses is regulated by the dopamine transporter (DAT). We hereinafter present significant differences between a sample of 15 treatment-seeking GD subjects and 17 healthy controls in terms of striatal DAT availability, and we explore its association with reward-based decision making. We performed ^{123}I-FP-CIT Single-photon emission computed tomography (SPECT) and correlated DAT binding ratios in the bilateral caudate and putamen with gambling symptoms (G-SAS, PG-YBOCS) and behaviors, as well as other psychometric variables (anhedonia and impulsivity). Gambling disorder (GD) subjects were also administered a computerized version of the Iowa gambling task (IGT) to assess reward-based decision making. We found reduced DAT availability in GD subjects compared with healthy controls (−13.30% in right caudate, −11.11% in right putamen, −11.44% in left caudate, and −11.46% in the left putamen). We also found that striatal DAT availability was inversely correlated with days spent gambling and IGT performance in GD subjects. These results provide evidence for a presynaptic dopaminergic dysfunction in striatal regions of GD subjects. Functional DAT down-regulation possibly sustains the transition towards compulsive gambling addiction, characterized both by hyperdopaminergic and hypodopaminergic states in the context of a sensitized dopaminergic system.

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Aims

Investigate striatal DAT availability in GD and HC subjects, using ^{123}I-FP-CIT SPECT;

Assess the impact of DAT availability on reward-based decision-making, as measured by the Iowa Gambling Task;

Highlight possible correlations between DAT availability and GD symptoms and behavior 15 treatment seeking, drug-free GD subjects (14 M, 1 F) and 17 matched HC (age, gender, level of education and ethnicity).

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Methods

ORIGINAL ARTICLE

WILEY Addiction Biology

Striatal presynaptic dopaminergic dysfunction in gambling disorder: A ^{123}I-FP-CIT SPECT study

Gambling symptoms	PG-YBOCS G-SAS TLFB-GD
Hedonic capacity	SHAPS VASa
Trait impulsivity	BIS-11
Decision-making	Iowa Gambling Task

Exclusion criteria

medication interfering with DAT binding
mental retardation
presence of a severe comorbid psychiatry condition
history of alcohol or substance addiction

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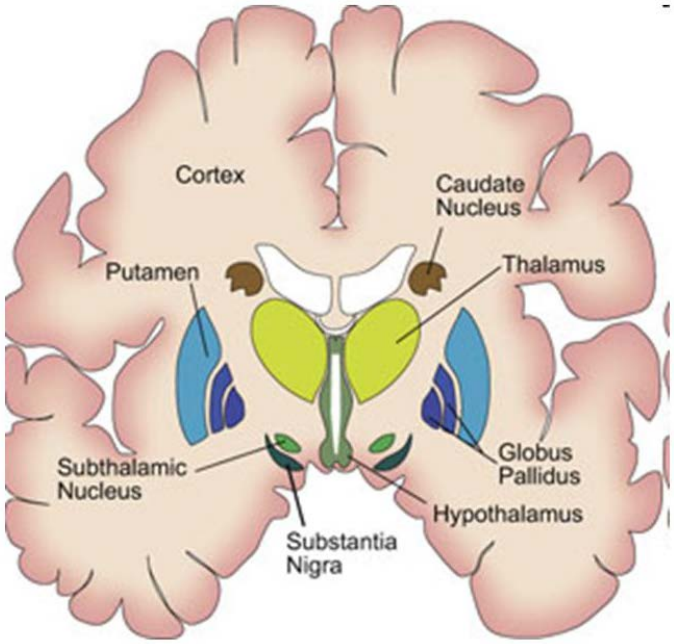
SPECT examination



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Valutazione SPECT cerebrale

- **Radiofarmaco impiegato** : 123I-FP-CIT (**Ioflupane**, marcato con Iodio^{123}, DaTSCAN ™, GE Healtcare)
- **Trattamento bloccante la captazione tiroidea** : somministrazione per os di perclorato di potassio (400 mg - 2 capsule di Pertiroid) 30 minuti prima dell'iniezione del radiofarmaco

- **SPECT**: effettuata a distanza di 3 ore dalla somministrazione ev del radiofarmaco

- **Valutazione semiquantitativa**: rapporti di uptake nelle ROIs effettuato mediante software Basal Ganglia Matching Tool

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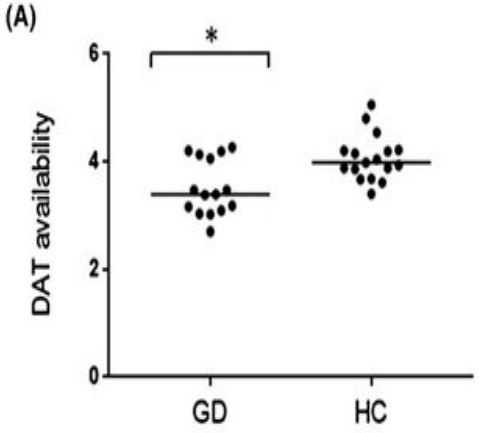
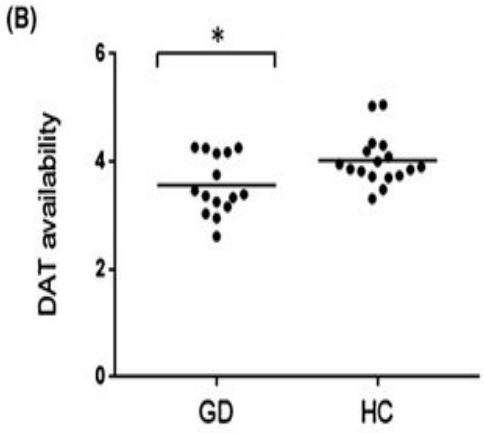
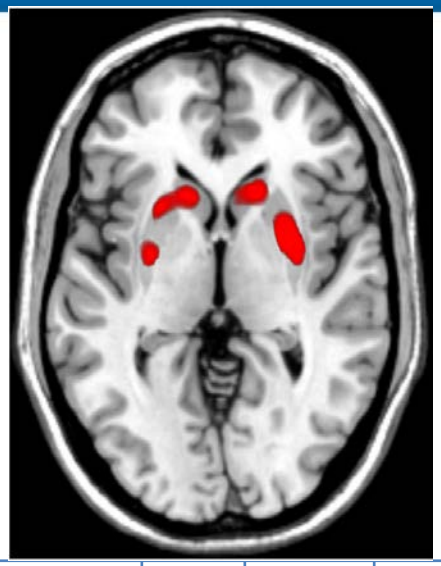
Lower DAT availability in striatal regions of GD subjects

A. Right caudate

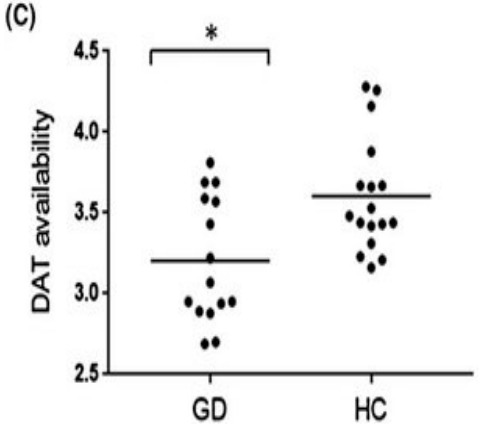


B. Left caudate

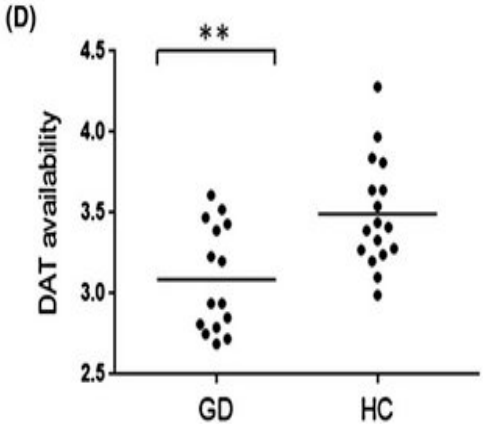




C. Right putamen



D. Left putamen



	GD	HC	Δ%	Sig.
R Caudate	3.52	4.06	**-13.3%**	.011
R Putamen	3.20	3.60	**-11.1%**	021
L Caudate	3.56	4.02	**-11.4%**	036
L Putamen	3.09	3.49	**-11.5%**	005

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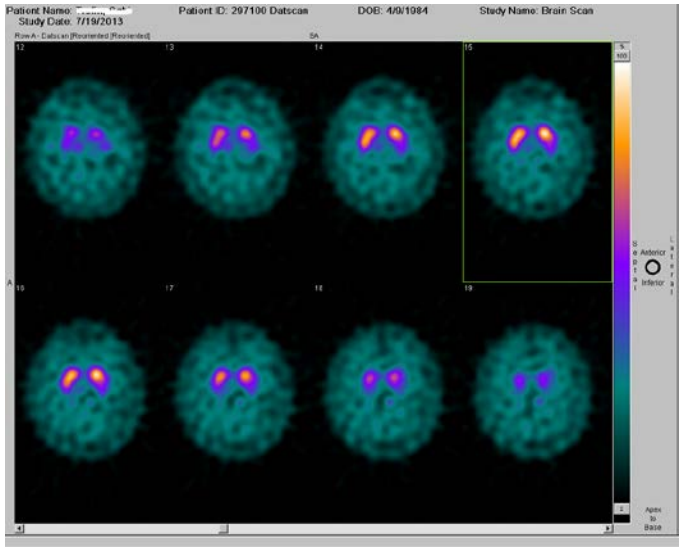
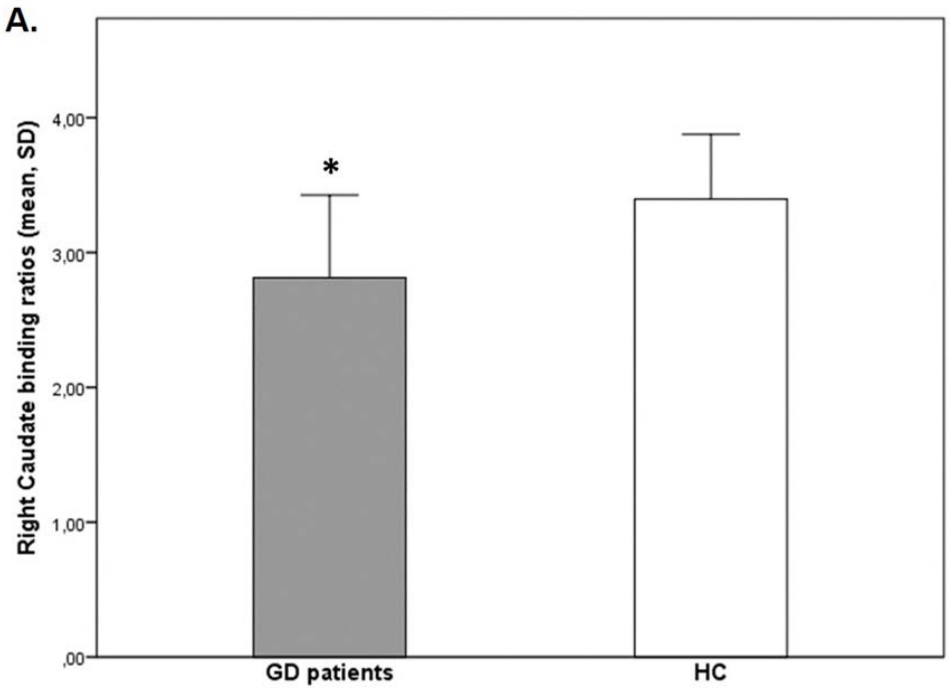
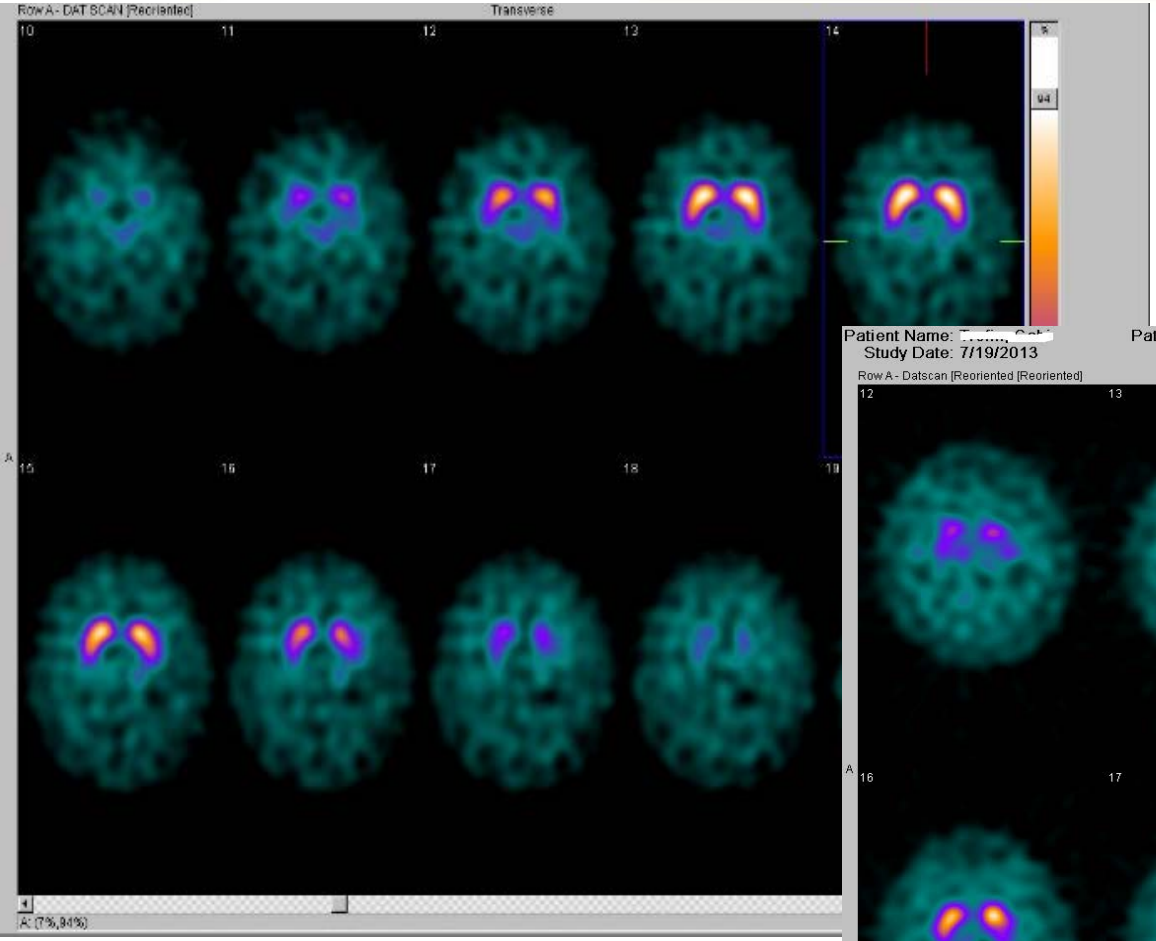
DAT binding in Gambling Disorder

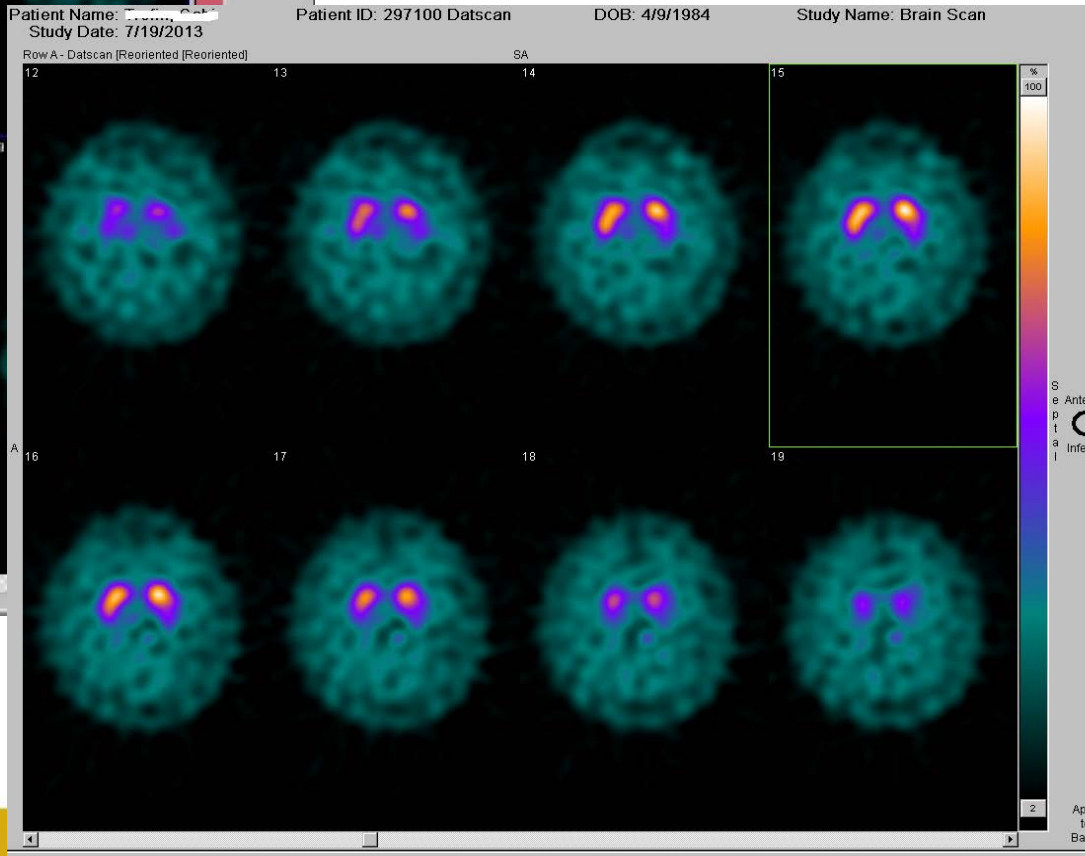




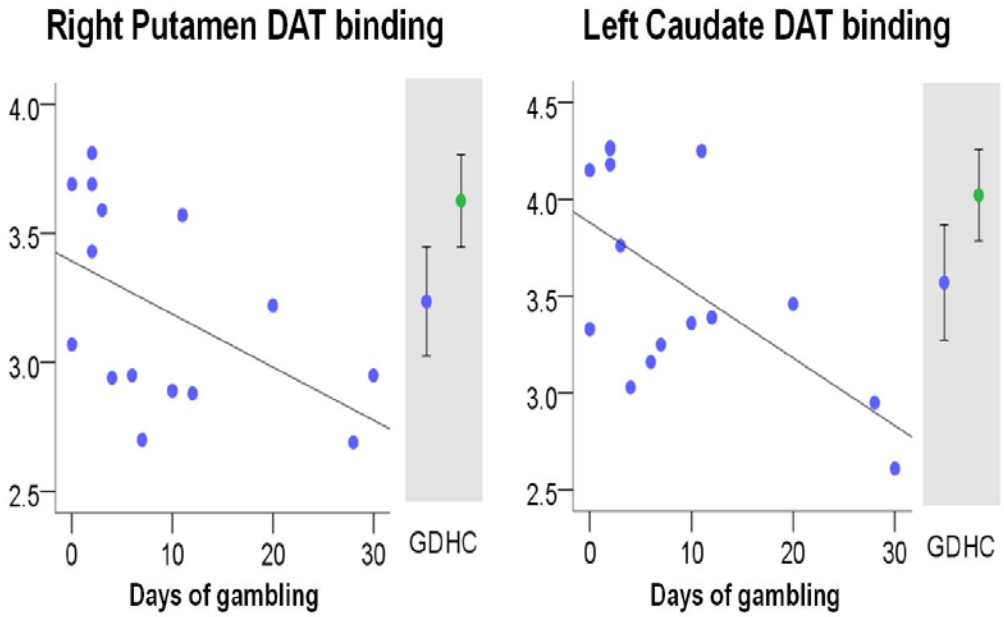
DAT binding in Gambling Disorder



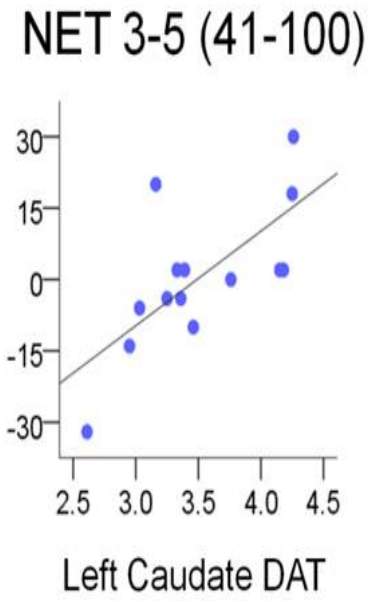
Controllo sano, M, 39 anni



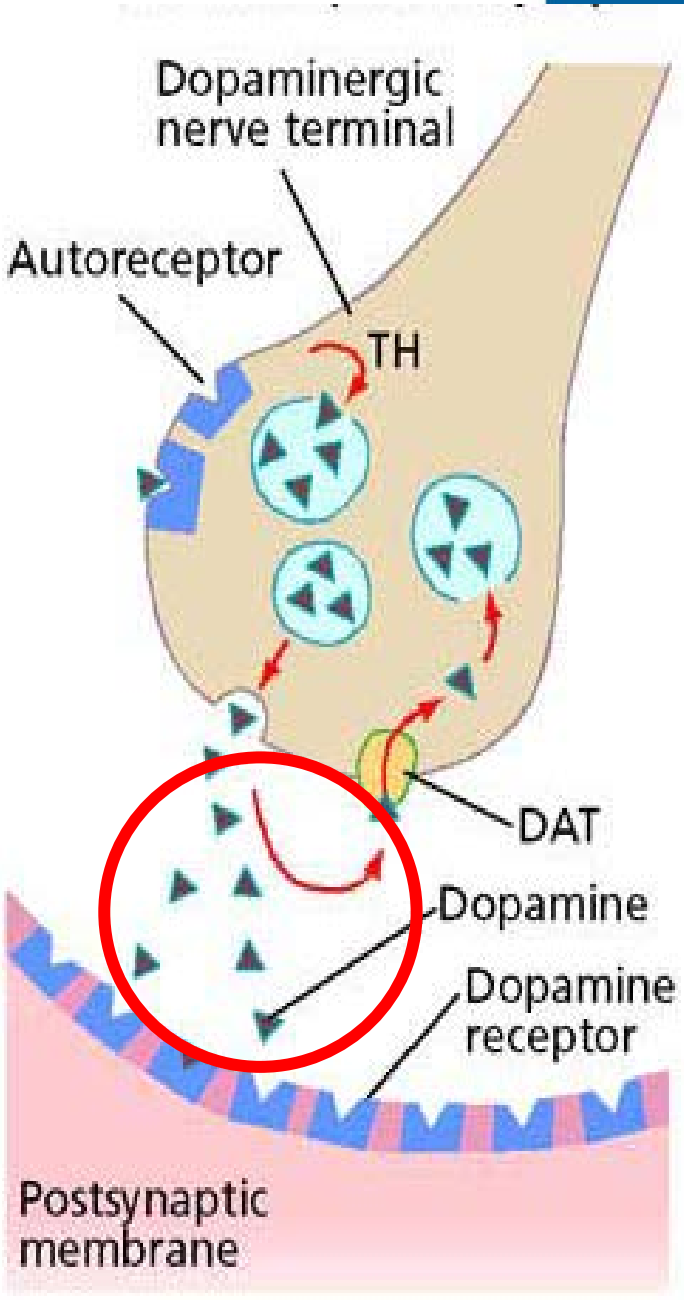
Giocatore d'azzardo patologico, M, 29 anni



DAT levels in the right putamen and left caudate were inversely correlated with number of days spent gambling in the last month



Lower striatal DAT binding was associated with poor performance on the Iowa Gambling Task (reward-based decision-making)



The finding of reduced DAT availability confirms the central role of dopaminergic dysregulation in GD

Gambling “high” may be underpinned by higher dopamine release or longer persistence of dopamine in the synapsis

GD is characterized both by hyper- and hypodopaminergic states (i.e. gambling withdrawal), as part of a sensitized dopaminergic system

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Dopamine and IGT

Executive functions are known to involve DA that contributes to synaptic plasticity in the striatum and the PFC

Synaptic plasticity is critically dependent on tonic extracellular DA concentration

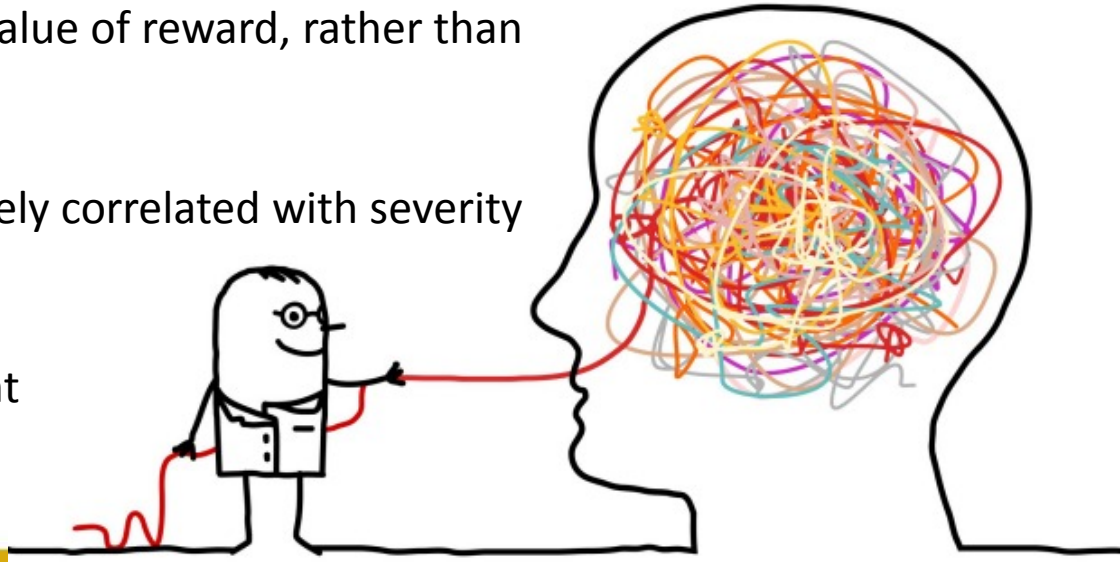
High performance on the IGT possibly reflects more preserved DA function

Greater striatal DA release has been found to predict worse IGT performance in GD

DA codes uncertainty and expected value of reward, rather than reward itself

Striatal DA release magnitude positively correlated with severity of gambling symptoms

DA release correlated with excitement



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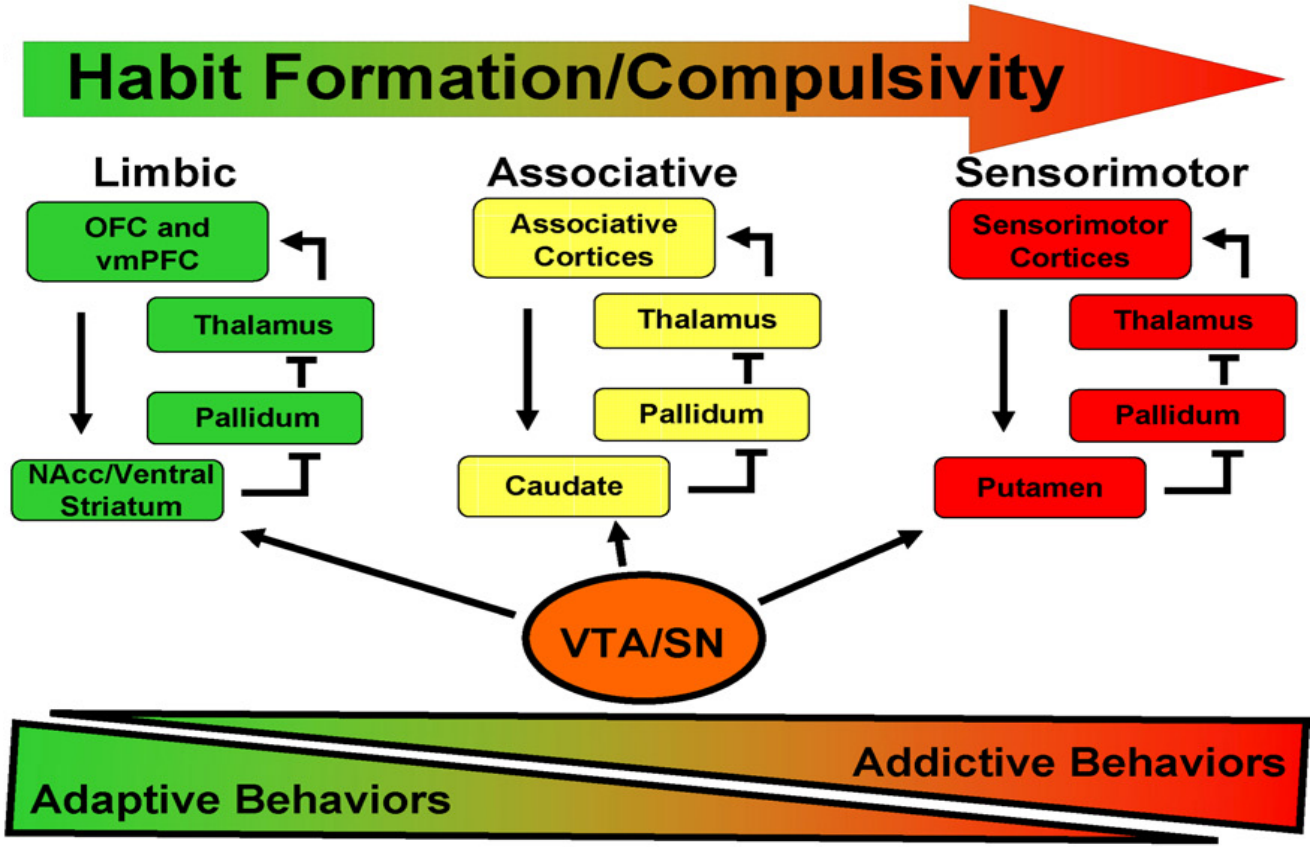
The Addictive Process: from Impulsivity to Compulsivity



(Brewer and Potenza, 2008; Biochemical Pharmacology 75:63–75)

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Impulsivity, a Heterogeneous Construct

- Support for impulsivity as a personality characteristic of pathological gamblers, rather than transient impulsive behavior, comes from numerous study over the years.

- In a recent study of 37 pathological gamblers, authors found that trait, rather than state, impulsivity is associated with Gambling Disorder.

(Odlaug, Schreiber, Grant, 2013; Current Opinion in Psychiatry 26:107-12)

Available online at www.sciencedirect.com
SCIENCE DIRECT
Comprehensive Psychiatry 47 (2006) 350–356
Comprehensive PSYCHIATRY
www.elsevier.com/locate/comppsych

The dimensional assessment of personality in pathologic and social gamblers: the role of novelty seeking and self-transcendence

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Abstract

Objective: A few personality traits are characteristic of pathologic gamblers (PGs), but it is not clear if and how their personality profile differs from that of non-pathologic gamblers (non-PGs).
Methods: Sixty-five non-clinical subjects, differentiated into non-PGs and PGs with the means of the South Oak Gambling Screen (SOGS) and *Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition–Text Revision* (*DSM-IV-TR*) criteria, were administered with the Temperament and Character Inventory; their values were compared with those of control subjects (CS).
Results: Novelty seeking (NS) and self-transcendence (ST) values were higher whereas self-directedness and cooperativeness values were lower in PGs with respect to both non-PGs and CS. A positive correlation was noted between SOGS score and NS ($r = 0.40$) and ST ($r = 0.50$) values, as well as a significant positive dependence between SOGS score and a family history of gambling ($t = 2.816$; $P = .007$). The subsamples of PGs reporting a parental involvement in gambling showed higher NS than the remaining PGs.
Conclusions: Specific temperamental and character dimensions, especially NS and ST, differentiated PGs from both non-PGs and CS; the identification of a personality profile at risk for problem gambling may represent an important predictor of outcome and constitute a possible target for specific treatment approaches.

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Psychiatry Research

December 30, 2016 Volume 246, Pages 789–795

Impulsivity, alexithymia and dissociation among pathological gamblers in different therapeutic settings: A multisample comparison study

Alessio Gori, Giuseppe Craparo, Vincenzo Caretti, Marco Giannini, Giuseppe Iraci-Sareri, Angelo Bruschi, Luigi Janiri, Lucia Ponti, Franca Tani

- Since many psychopathological traits seem to be related to Gambling Disorder (GD), impulsivity, alexithymia and dissociation could play a central role in gambling behaviors, particularly in pathological gambling. We test this hypothesis in four distinct samples of gamblers, three undergoing different types of treatments and a control group. The study sample consists of 204 subjects (males 87.3%, mean age=47.75 years, SD=12.08) divided into four groups: (1) 59 subjects belonging to an Outpatients Treatment Program in the National Health System (NHS); (2) 60 subjects of an Outpatients Self-Help Group Program; (3) 35 subjects belonging to a Residential Treatment Program (Inpatients Program); and (4) 50 subjects without gambling problems (Control Group). Results show a positive relationship between gambling behaviors, impulsivity and alexithymia, and a negligible link between gambling behaviors and dissociation. Findings also display the presence of higher levels of all these features in pathological gamblers with higher scores on the SOGS, and particularly, in participants attending a Residential Treatment Program (Inpatients Program). This study confirms the hypothesis of the presence of higher levels of impulsivity, alexithymia and dissociation in pathological gamblers with a greater severity and seems to indicate a significant importance of impulsivity and alexithymia in predicting gambling behaviors.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 01 December 2017
doi: 10.3389/fpsyt.2017.00256

Gender Differences and Psychopathological Features Associated With Addictive Behaviors in Adolescents

Marco Di Nicola[1], Vittoria Rachele Ferri[1], Lorenzo Moccia[1], Isabella Panaccione[2], Annamaria Miriam Strangio[1], Daniela Tedeschi[1], Paolo Grandinetti[1], Antonino Callea[3], Fabio De-Giorgio[4], Giovanni Martinotti[5] and Luigi Janiri[1]**

A sample of high school Italian students **(n =996; M=240, F=756)** was examined using a self-report survey concerning socio-demographic characteristics, cigarette smoking, alcohol and substance use, perceived academic performance, activities, and behaviors **(Internet use, gambling, and physical exercising).** Moreover, different psychometric scales were employed to investigate psychopathological dimensions. Our study showed a relevant prevalence of addictive behaviors in a sample of Italian high school students, with specific gender differences. A significant association between substance-/non-substance-related addictive behaviors and psychopathological dimensions was found, including **dissociative proneness, anhedonia, alexithymia, and impulsivity**. Besides, addictive behaviors were significantly more frequent among students reporting poor school performance.

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Implications of PG-AUD comorbidity

- More difficult to treat and retain: 2x rate of dropout
- Lower compliance rates
- Other comorbidities likely
- More likely to relapse

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Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Co-occurrence of alcohol use disorder and behavioral addictions: relevance of impulsivity and craving

Marco Di Nicola[a,b,*], Daniela Tedeschi[a], Luisa De Risio[a], Mauro Pettorruso[a], Giovanni Martinotti[c], Filippo Ruggeri[a], Kevin Swierkosz-Lenart[d], Riccardo Guglielmo[a], Antonino Callea[e], Giuseppe Ruggeri[a], Gino Pozzi[a], Massimo Di Giannantonio[c], Luigi Janiri[a,b]

- 116 AUD outpatients and 189 healthy controls (HC)
- Diagnostic criteria and specific tests for pathological gambling, compulsive buying, sexual, internet and physical exercise addictions; BIS-11; TCI-R; OCDS; VASc.

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- Evaluate the occurrence of Gambling Disorder (GD) and other behavioral addictions (BAs) in subjects with Alcohol Use Disorder (AUD) and to investigate the role of impulsivity, personality dimensions and craving

AUD subjects (n=116)	**Single BA (n=23)**	**Multiple BAs (n=11)**					**Total (n=34)**	**(%)**
		+GD	***+CB***	***+SA***	***+IA***	***+EA***		
GD	3	-	6 [a]	1 [a]	-	-	9	7.7
CB	13	6 [a]	-	3 [a]	-	3	24	20.7
SA	6	1 [a]	3 [a]	-	-	-	9	7.7
IA	0	-	-	-	-	-	0	0
EA	1	-	3	-	-	-	4	3.5
HC subjects (n=189)	**Single BA (n=17)**	**Multiple BAs (n=1)**					**Total (n=19)**	**(%)**

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- 29.3% (n=34) of AUD subjects had at least one BA
- AUD patients obtained higher scores than the control group in the BA tests, except for physical exercise and internet addiction tests
- The BIS-11, OCDS and VASc scores were significantly higher in AUD subjects with at least a co-occurring BA compared to those without it
- AUD subjects with lower BIS-11 and VASc scores showed a minor risk to develop a BA
- **High levels of impulsivity** and **craving** for alcohol seem to be associated with other BA, supporting the hypothesis that addiction is a unitary process

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GD and mood disorders comorbidity

Journal of Affective Disorders 125 (2010) 82–88

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

Behavioural addictions in bipolar disorder patients: Role of impulsivity and personality dimensions

Marco Di Nicola*, Daniela Tedeschi, Marianna Mazza, Giovanni Martinotti, Desiree Harnic, Valeria Catalano, Angelo Bruschi, Gino Pozzi, Pietro Bria, Luigi Janiri

Institute of Psychiatry, Bipolar Disorder Unit, Catholic University Medical School, Rome, Italy

158 bipolar euthymic outpatients vs. 200 matched healthy controls

Bipolar diagnosis: BP-I: 71 (45%), BP-II: 44 (28%), CtD: 43 (27%)

33% of BD patients presented at least one BA, as compared to 13% of controls

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- 33% of BD patients presented at least one BA, as compared to 13% of controls

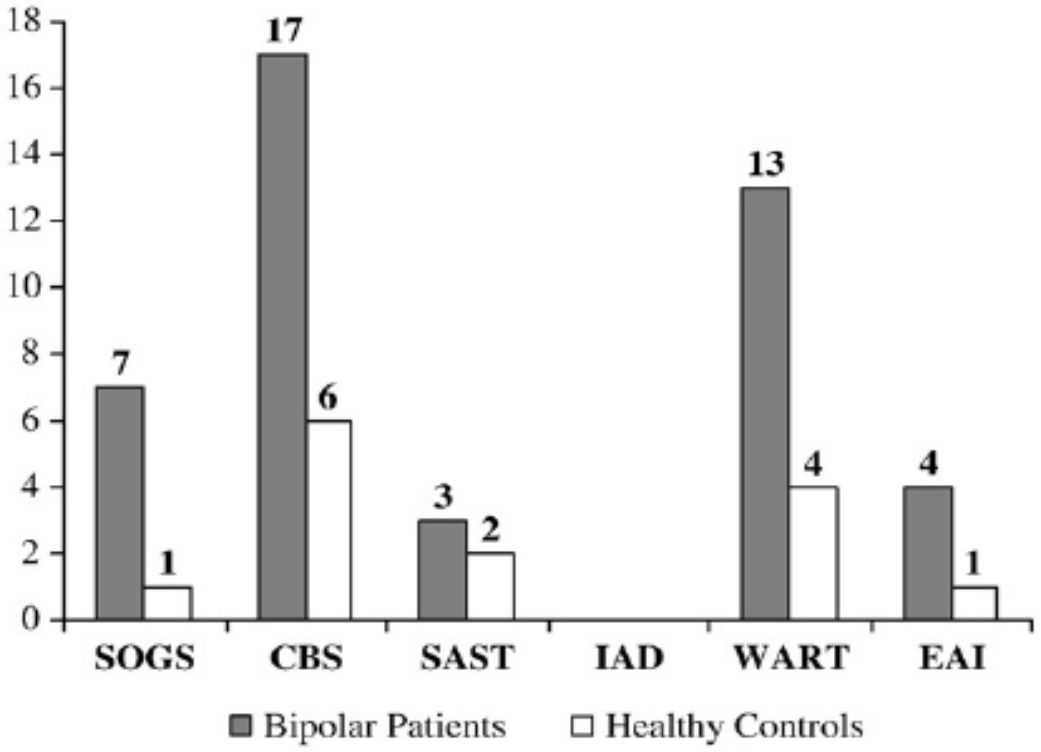

Fig. 1. Percentages of subjects that reach the cut-off at the questionnaires for the screening of behavioural addictions. Legend: SOGS: The South Oaks Gambling Screen; CBS: Compulsive Buying Scale; SAST: Sexual Addiction Screening Test; IAD: Internet Addiction Disorder test; WART: Wart Addiction Risk Test; EAI: Exercise Addiction Inventory.

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L'efficacia del trattamento in DH

Obiettivi dello studio:

1. *Valutare l'efficacia del trattamento*
2. *Valutare l'impatto della comorbidità psichiatrica sull'esito*
3. *Individuare predittori d'esito negativo*

Campione: **148 pazienti** con **diagnosi di GAP** arruolati presso il D.H. 2013-14

Strumenti utilizzati:

- *M.I.N.I. (Mini-International Neuropsychiatric Interview)*
- *TCI (Temperament and Character Inventory)*
- *BIS-11 (Barratt Impulsiveness Scale)*
- *ASI (Addiction Severity Index)*
- *G-SAS (Gambling Symptoms Assessment Scale)*
- *VAS Craving (Visual Analogue Scale)*

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Predittori di outcome negativo

- Comorbidità con disturbi da uso di sostanze: 78% ($p<0.01$)
- Non aderenza al trattamento farmacologico se prescritto: 75% ($p<0.01$)
- Disturbo antisociale di personalità: 66% ($p<0.05$)
- Persistenza del craving alla valutazione T1 ($p<0.05$)

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Dopaminergic and clinical correlates of high-frequency repetitive transcranial magnetic stimulation in gambling addiction: a SPECT case study

- **Addictive Behaviors** Volume 93, June 2019, Pages 246-249

- Mauro Pettorruso[a] Daniela Di Giuda[bc] Giovanni Martinotti[ad] Fabrizio Cocciolillo[b] Luisa De Risio[e] Chiara Montemitro[a] Giovanni Camardese[e] Marco Di Nicola[e] Luigi Janiri[e] Massimo di Giannantonio[a] NST Study Group[1]

- https://doi.org/10.1016/j.addbeh.2019.02.013Get rights and content

- **Highlights**
- We described cessation of gambling behavior and craving in a GD patient over a six month follow up period after treatment with repetitive Transcranial Magnetic Stimulation (rTMS) over the left dorsolateral prefrontal cortex; no craving or relapses were reported over the six-month follow-up period.
- After two weeks of treatment, we found changes in DAT availability that possibly reflect dopaminergic pathways modulation by rTMS.
- Neuromodulation of brain circuitries implicated in the executive control network may impact the clinical course of GD.

Trattamenti farmacologici

Opioid antagonists

Study	Drug tested and mean-range dosage	Study design	Study group and duration	Findings
		Opioid antagonists in GD		
Kim et al. 2001 [15]	Naltrexone mean dose 188 mg/day	Double-blind placebo-controlled	89 patients for 12 weeks	Naltrexone is significantly superior to placebo
Grant et al. 2008 [29]	Naltrexone 50–150 mg/day	Double-blind placebo-controlled	77 patients for 18 weeks	Naltrexone is significantly superior to placebo
Toneatto et al. 2009 [30]	Naltrexone mean dose 59 mg/day	Double-blind placebo-controlled	52 patients for 11 weeks	Naltrexone is not significantly superior to placebo
Grant et al. 2006 [16]	Nalmefene 25–100 mg/day	Double-blind placebo-controlled	207 patients for 16 weeks	Nalmefene is significantly superior to placebo
Grant et al. 2010 [33]	Nalmefene 20–40 mg/day	Single-blind *for 1 week with placebo* Double-blind placebo-controlled *for 15 weeks*	233 patients for 16 weeks	Nalmefene 40 mg/day is significantly superior to placebo

Trattamenti farmacologici

Hindawi Publishing Corporation
BioMed Research International
Volume 2014, Article ID 109786, 11 pages
http://dx.doi.org/10.1155/2014/109786

Review Article

Targeting the Glutamatergic System to Treat Pathological Gambling: Current Evidence and Future Perspectives

Mauro Pettorruso,[1] Luisa De Risio,[1] Giovanni Martinotti,[2] Marco Di Nicola,[1] Filippo Ruggeri,[1] Gianluigi Conte,[1] Massimo Di Giannantonio,[2] and Luigi Janiri[1]

- 19 studies have been included
- Clinical trials and case series using glutamatergic drugs to treat GD
- To elucidate the effectiveness on gambling behaviors and on the related clinical dimensions (craving, withdrawal, and cognitive symptoms)

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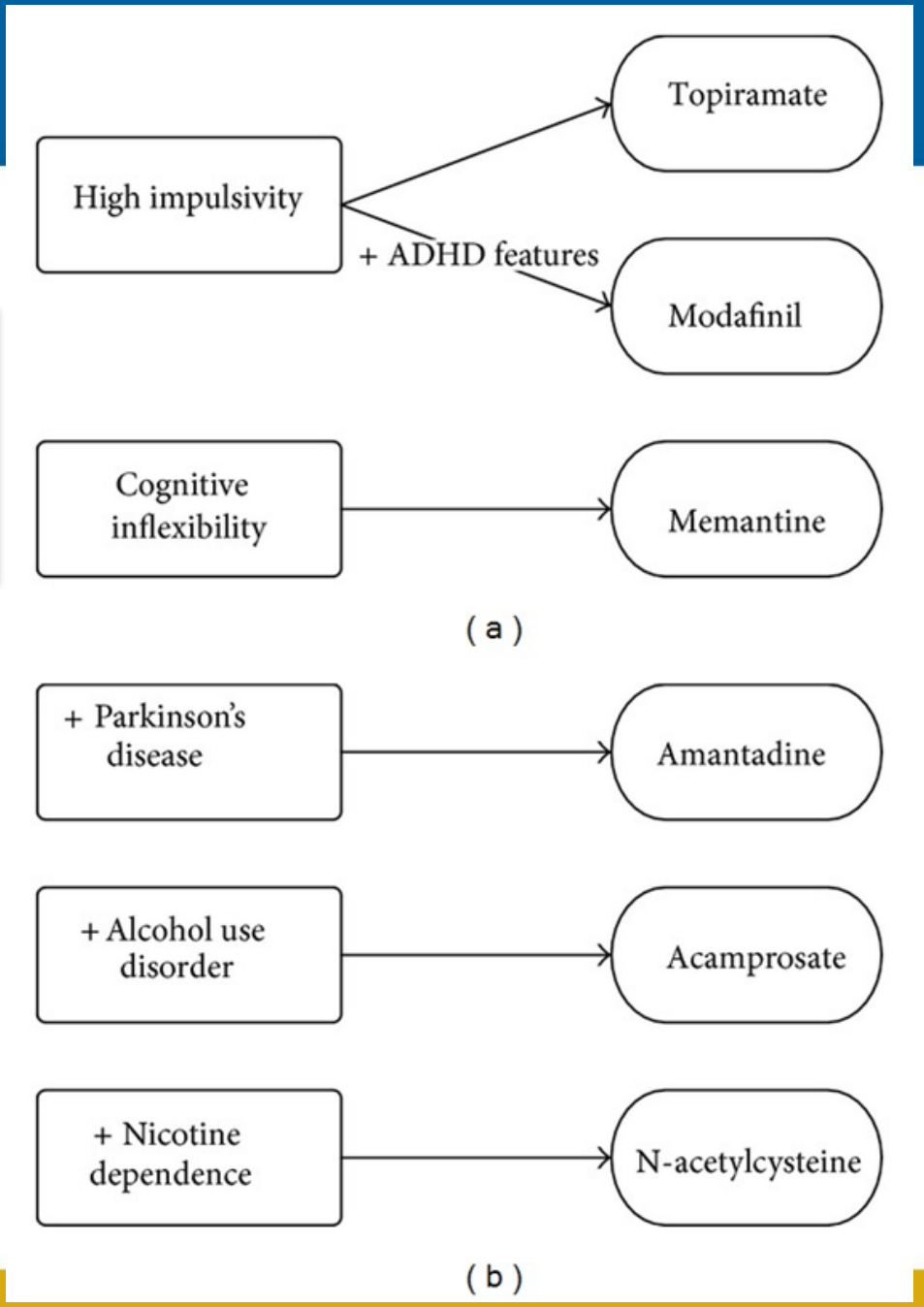
Review Article

Targeting the Glutamatergic System to Treat Pathological Gambling: Current Evidence and Future Perspectives

Mauro Pettorruso,[1] Luisa De Risio,[1] Giovanni Martinotti,[2] Marco Di Nicola,[1] Filippo Ruggeri,[1] Gianluigi Conte,[1] Massimo Di Giannantonio,[2] and Luigi Janiri[1]



Selection of glutamatergic treatment strategies to treat GD:

(a) Clinical domains

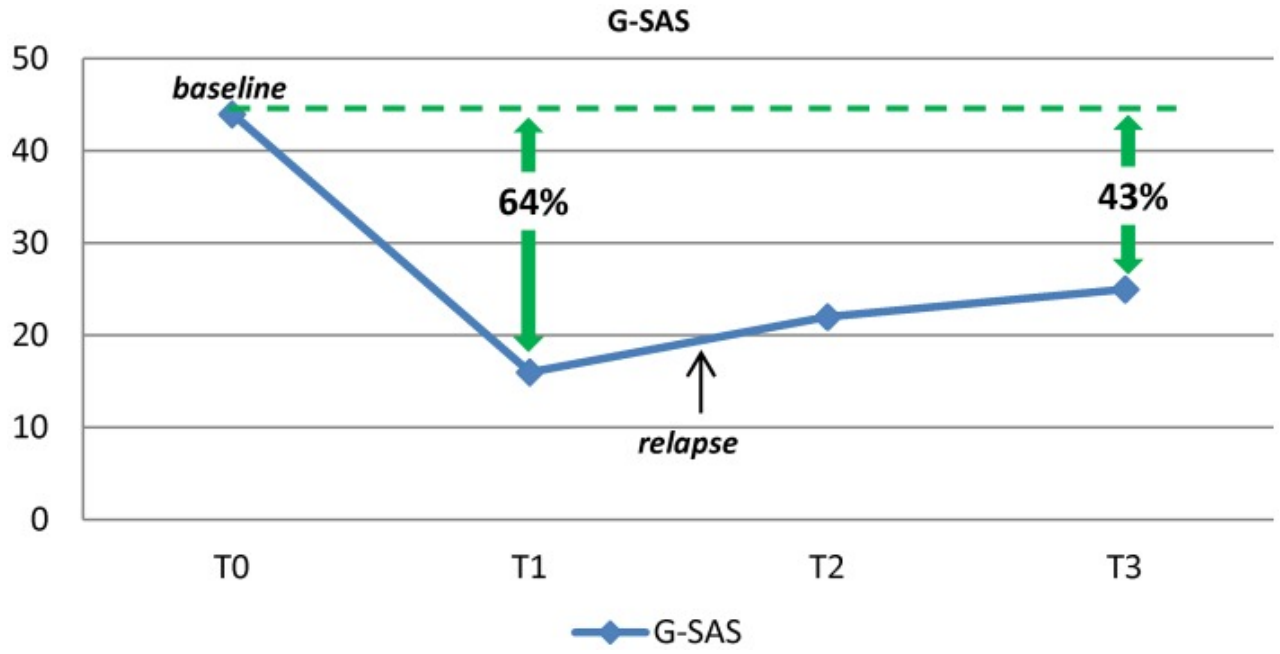
(b) Comorbidity issues

frontiers in PSYCHIATRY

CLINICAL CASE STUDY
published: 27 November 2012
doi: 10.3389/fpsyt.2012.00102

Amantadine in the treatment of pathological gambling: a case report

Mauro Pettorruso[1], Giovanni Martinotti[2], Marco Di Nicola[1], Marco Onofrj[3], Massimo Di Giannantonio[2], Gianluigi Conte[1] and Luigi Janiri[1]*



Our result is discussed in the context of the glutamatergic hypothesis of addiction. The role of the dopaminergic system, and its interaction with the glutamatergic system, is also explored.

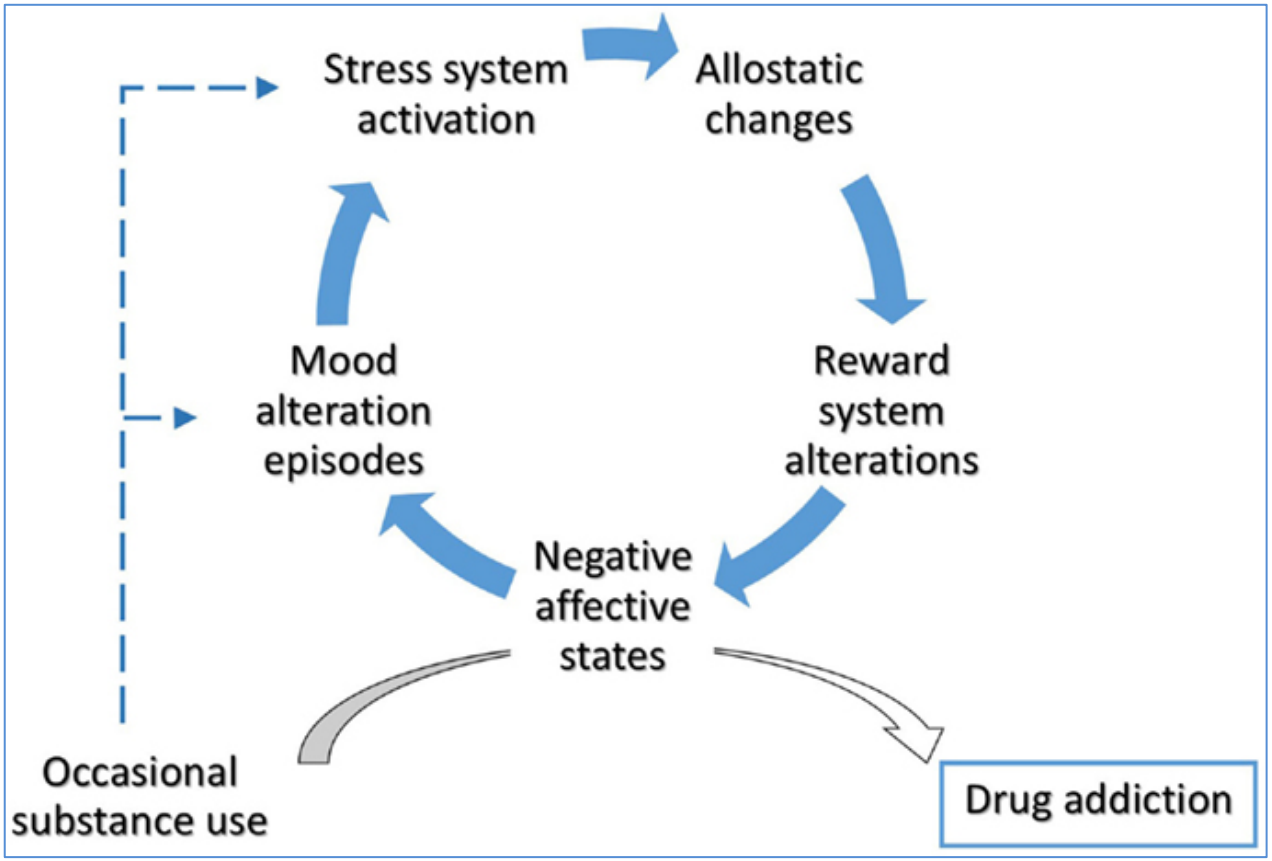
frontiers in PSYCHIATRY

PERSPECTIVE ARTICLE
published: 03 December 2014
doi: 10.3389/fpsyt.2014.00173

Allostasis as a conceptual framework linking bipolar disorder and addiction

Mauro Pettorruso[1]*, Luisa De Risio[1], Marco Di Nicola[1], Giovanni Martinotti[2], Gianluigi Conte[1] and Luigi Janiri[1]

[1] Department of Neuroscience, Institute of Psychiatry and Clinical Psychology, Catholic University of Sacred Heart, Rome, Italy
[2] Department of Neuroscience and Imaging, Institute of Psychiatry, "G. d'Annunzio" University of Chieti-Pescara, Chieti, Italy



Journal of Affective Disorders 167 (2014) 285–298

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Review

Bipolar disorder and gambling disorder comorbidity: Current evidence and implications for pharmacological treatment

Marco Di Nicola [a,b,*], Luisa De Risio [a], Mauro Pettorruso [a], Giulio Caselli [a], Franco De Crescenzo [a,c], Kevin Swierkosz-Lenart [d], Giovanni Martinotti [e], Giovanni Camardese [a], Massimo Di Giannantonio [e], Luigi Janiri [a,b]

[a] Institute of Psychiatry and Clinical Psychology, Catholic University of Sacred Heart, Rome, Italy
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[d] Centre neuchâtelois de psychiatrie, République et Canton de Neuchâtel, Switzerland
[e] Department of Neuroscience and Imaging, Institute of Psychiatry, "G. d'Annunzio" University of Chieti-Pescara, Italy

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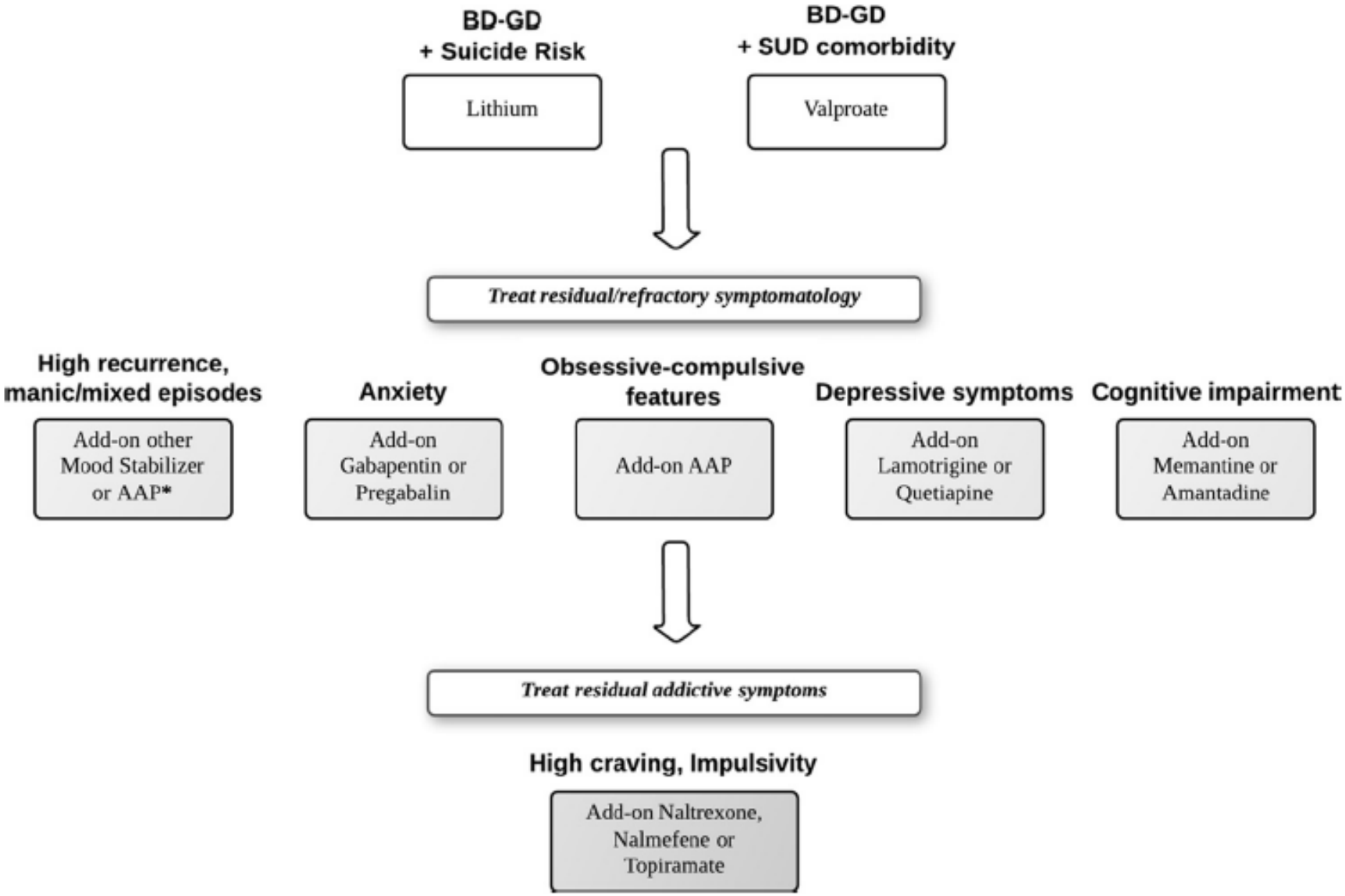
Proposal of an algorithm for the treatment of BD-GD comorbidity



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Gamblig-related Cognitive Distorsions

- These distortions refer to how the gambler thinks about randomness, chance and skills and foster an inappropriately high expectation of winning during the game:
  - *Gambler's Fallacy*: it's a bias in the processing of random sequences. The expectancy of a certain event (e.g., heads in a coin flip) become less likely after a long series of the same event (e.g., three successive tails). The cognitive distortion concerns the belief that a short segment of a random sequence should reflect the overall distribution.

(Clark et al., 2013; The Journal of Neuroscience 43:17617-17623)

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Gamblig-related Cognitive Distorsions

- *Illusions of Controls:* this term refers to the interpretation of skill involvement in situations that are governed by chance alone. A recent study using a contingency judgment task, found that pathological gamblers displayed a greater tendency to overestimate their control of positive outcomes than non-gambling participants.

- *Near Miss*: unsuccessful outcomes that are proximal to a major win. Using a slot machine task that delivered occasional jackpot wins, near misses (where the reels landed adjacent to a win) were associated with higher self reported motivations to gamble than full-miss outcomes, despite their equivalence as nonwins.

(Clark et al., 2013; The Journal of Neuroscience 43:17617-17623)

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Problem gamblers share deficits in impulsive decision-making with alcohol-dependent individuals

Lawrence et al., 2009. Addiction

PG and AD groups displayed impairments in risky decision-making and cognitive impulsivity (tasks linked to ventral prefrontal cortical dysfunction) relative to controls.

	PG (n = 21)[a]	*AD (n = 21)*[a]	*HC (n = 21)*[a]	*Test statistic*	*Post-hoc effects of group*
Cambridge Gamble Task					
Total points obtained	1772 ± 1205	1605 ± 805	1551 ± 592	$F_{(2,60)} = 0.34$, NS	–
Bankruptcies[b]	5 (24%)	4 (19%)	0 (0%)	$\chi^2(1) = 5.25$, $P = 0.022$	–
% Rational decisions	90 ± 19	94 ± 9	96 ± 9	$F_{(2,60)} = 1.15$, NS	–
Percentage wager	59 ± 17	56 ± 11	48 ± 13	$F_{(2,56)} = 3.31$, $P = 0.045$	PG>HC
Decision latency (ms)	2064 ± 739	2742 ± 1136	1970 ± 753	$F_{(2,56)} = 5.74$, $P = 0.005$	AD>[PG=HC]
Information Sampling Task					
Errors	5.0 ± 3.2	4.8 ± 2.5	3.2 ± 2.4	$F_{(2,60)} = 2.41$, $P = 0.099$	PG>HC
Boxes opened (/25)	8.6 ± 3.6	9.8 ± 4.1	12.8 ± 4.6	$F_{(2,60)} = 5.92$, $P = 0.005$	[PG=AD]<HC
Spatial working memory					
Total errors	23.3 ± 22.8	40.3 ± 30.0	22.8 ± 21.4	$F_{(2,57)} = 3.20$, $P = 0.048$	AD>[PG=HC]
Strategy	32.0 ± 6.2	31.8 ± 8.5	29.5 ± 5.4	$F_{(2,57)} = 0.73$, NS	–
Digit span					
Forwards score (/12)	9.7 ± 1.8	8.3 ± 1.9	10.1 ± 1.8	$F_{(2,57)} = 5.30$, $P = 0.008$	AD<[PG=HC]
Backwards score (/12)	8.6 ± 3.0	6.5 ± 2.2	7.8 ± 2.5	$F_{(2,57)} = 3.51$, $P = 0.037$	AD<PG

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Neuroscience and Biobehavioral Reviews 78 (2017) 104–116

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Neural correlates of cognitive control in gambling disorder: a systematic review of fMRI studies

Lorenzo Moccia[a,1], Mauro Pettorruso[a,1], Franco De Crescenzo[a], Luisa De Risio[a], Luigi di Nuzzo[a,b], Giovanni Martinotti[c], Angelo Bifone[d], Luigi Janiri[a], Marco Di Nicola[a,*]

[a] Institute of Psychiatry and Psychology, Fondazione Policlinico Universitario "A.Gemelli", Università Cattolica del Sacro Cuore, Largo Francesco Vito 1, 00168 Rome, Italy
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[d] Istituto Italiano di Tecnologia, Center for Neuroscience and Cognitive Systems, Corso Bettini 31, 38068, Rovereto, Italy

We conducted a comprehensive literature search and collected neuropsychological and neuroimaging data investigating cognitive control in GD. We included a total of 14 studies comprising 499 individuals.

Table 2
Differential fMRI activation patterns in cognitive control tasks in PG subjects vs healthy controls.

Cognitive task	Study		Prefrontal Cortex							Striatum		PC
			OFC/ VMPFC	SFG	MFG	DMPFC	VLPFC	DLPFC	ACC	VS	DS	
Response inhibition	de Ruiter et al. (2012)	*During successful response inhibition*				↓						
		During failed response inhibition							↓			
	van Holst et al. (2012a)	*Neutral go vs neutral no-go trials*						↑	↑ *right*			
		Positive no-go vs neutral no-go trials						↓		↓ *left*		
		Negative no-go vs neutral no-go trials						↓ *right*	↓ *left*			
		Gamble no-go vs neutral no-go trials						↓	↓ *right*			
Conflict monitoring	Potenza et al. (2003)	*Following presentation of incongruent stimuli*		↓ *left*	↓ *left*							
Decision making	Tanabe et al. (2007)	*During decision making*	↓						↓			
		During risky vs safe decks selection	↑						↑			
	Power et al. (2012)	*During risky vs safe decks selection*	↑ *right*	↑ *right*							↑ *right*	
	Brevers et al. (2016)	*During deck selection*	↓ *right*					↓ *right*		↑ *right*		
	Miedl et al. (2010)	*During low vs high-risk trials in a quasi-realistic black jack scenario*					↑ *right*					
		During gains vs losses										↑ *left*
	Gelskov et al. (2016)							~			~	
	Brevers et al. (2015)	*During decision making under risk vs decision making under ambiguity*									↓	
		During bet vs sure pay off options									↑	
Cognitive flexibility	Verdejo-Garcia et al. (2015)	*During reversal shifting vs perseveration*					↓ *right*					
	de Ruiter et al. (2009)	*During monetary loss and win*					↓ *right*					
Delay discounting	Miedl et al. (2012)	*As correlated with subjective value representation of risky and delayed rewards*	~						~	~		
	Miedl et al. (2015)	*During the comparison of LDR and SIR*						↑	↑			↑
	Hinvest et al. (2011)	*Positively correlated with impulsivity scores*					~		~			

Notes: ↑: increased activation; ↓: decreased activation; ~: increased or diminished correlation between fMRI activity of the selected areas and task response.

- Although definitive conclusions cannot be drawn, taken together, the results indicate that impaired activity in prefrontal areas, including **DLPFC**, **ACC** and **OFC/VMPFC**, may account for impaired cognitive control, contributing to some aspects of PG clinical phenomenology, such as those related to the progressive loss of control over gambling behaviors.

- On the one hand, an imbalanced activity in ventromedial prefrontal areas, including the medial part of **OFC** as well as the more ventral sectors of the **medial prefrontal cortex** and **ACC**, has been observed in most of the fMRI studies which have assessed *decision making* and *choice impulsivity*. On the other hand, an abnormal pattern of activity within dorsal and ventrolateral prefrontal regions including **DLPFC**, **DMPFC**, **dorsal ACC** and **VLPFC** has been described in those studies which have adopted *response inhibition* and *reversal learning* tasks, respectively.

- Among prefrontal regions, **orbital** and **ventromedial** areas seem to be a possible nexus for sensory integration, value based decision-making and emotional processing, thus contributing to both motivational and affective aspects of cognitive control.

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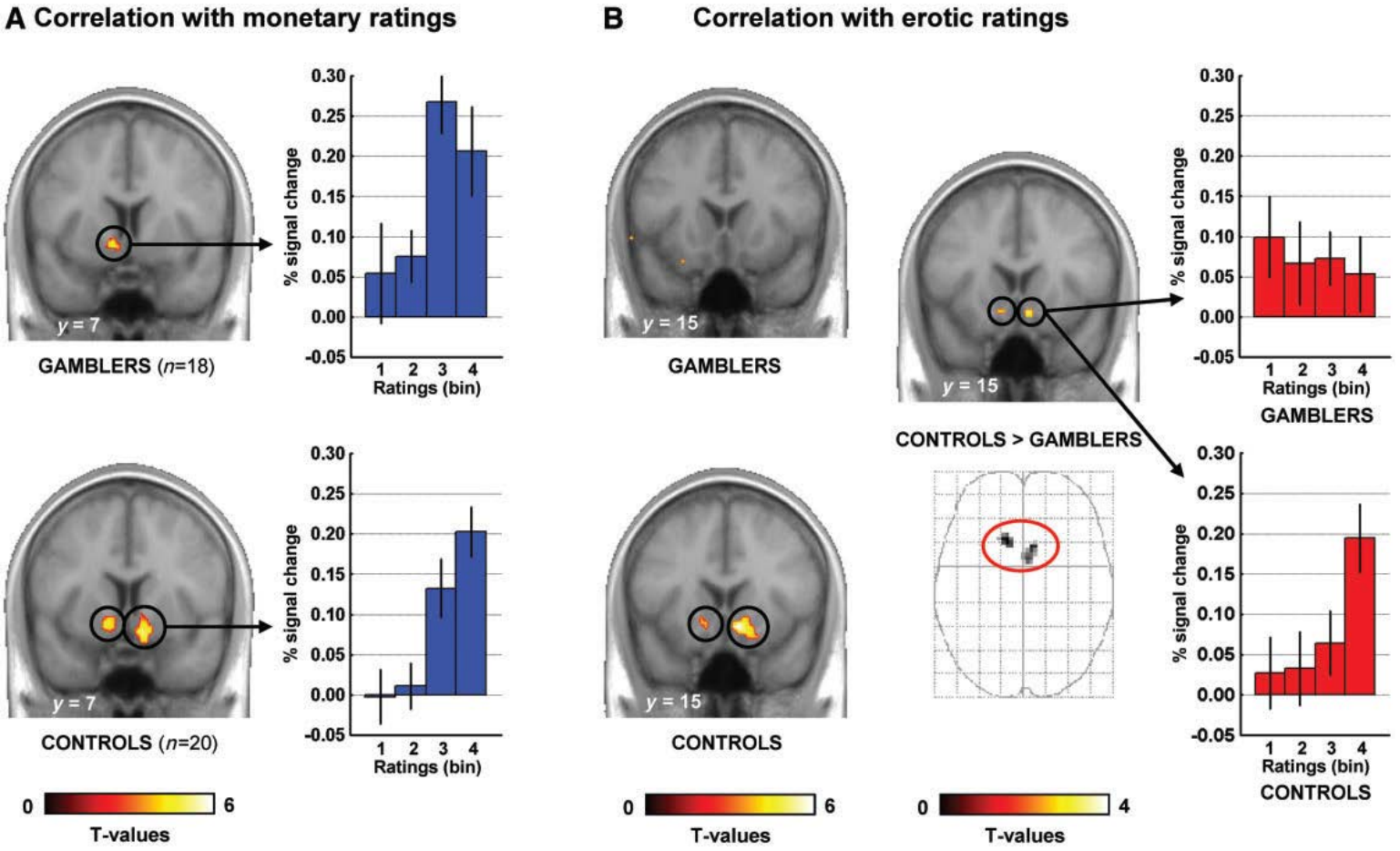
Ventral striatum activation to “natural” and “addiction related” rewards in pathological gamblers.



(Sescousse et al., 2013; Brain 136:2527-2538)

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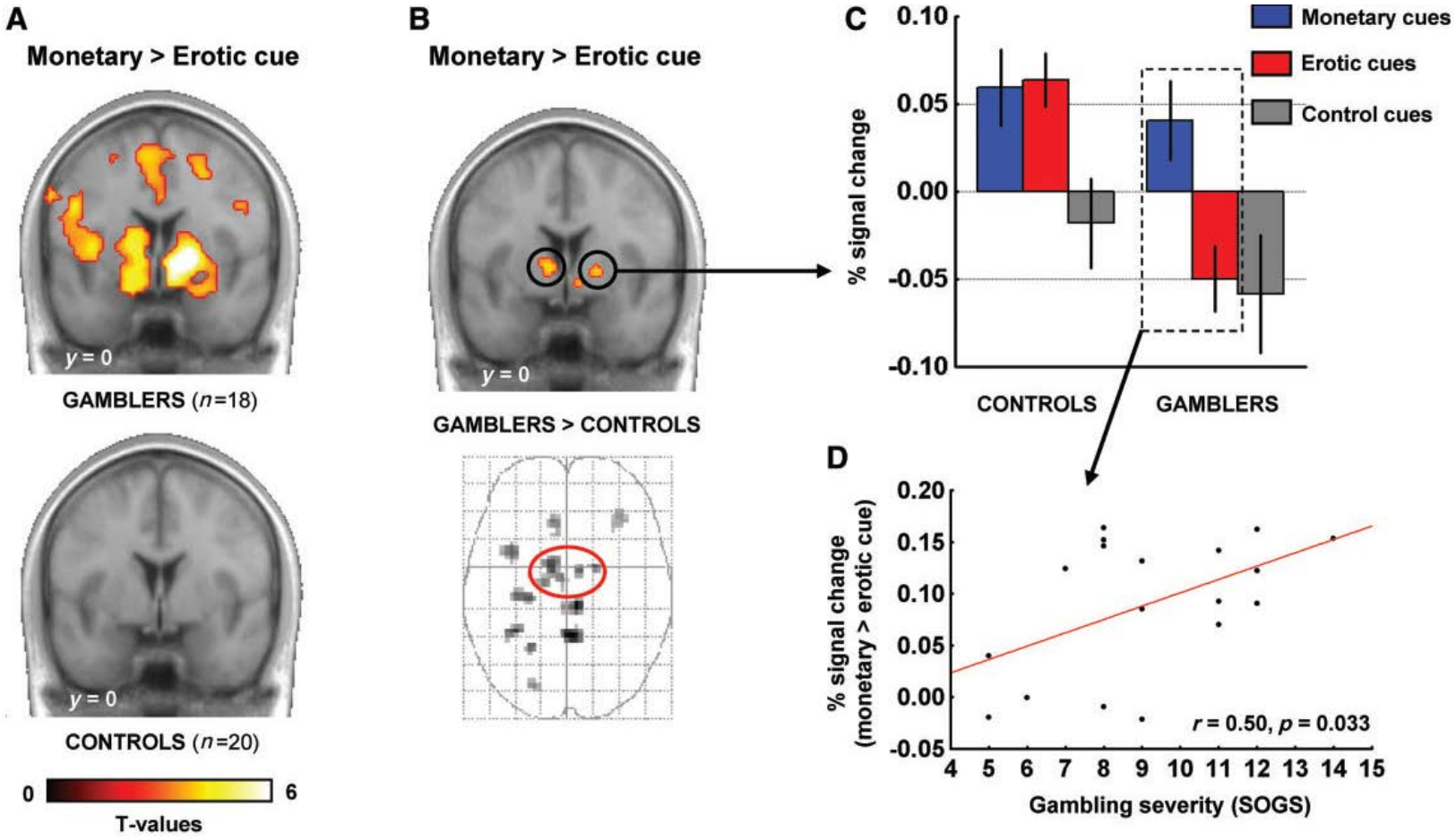
Ventral striatum activation to "natural" and "addiction related" rewards in pathological gamblers.



(Sescousse et al., 2013; Brain 136:2527-2538)

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Sensitivity to Rewards in Gambling

- It seems most likely that pathological gamblers are not suffering from a “reward deficiency” in general but that pathological gamblers have a different appraisal of gambling related stimuli, presumably caused by enhanced “incentive salience” of gambling related stimuli.

(Sescousse et al., 2013; Brain 136:2527-2538) (Clark et al., 2013; The Journal of Neuroscience)