Is Obesity a Brain Disease?

Evidence from behavioral, neuroimaging, and neurostimulation data

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Symposium: **HUNGRY BRAINS: FROM FOOD PERCEPTION TO FOOD ADDICTION**
SIPF November 10th 2023 Siena

Introduzione Generale (i)

Cibo vs. Sostanze di abuso

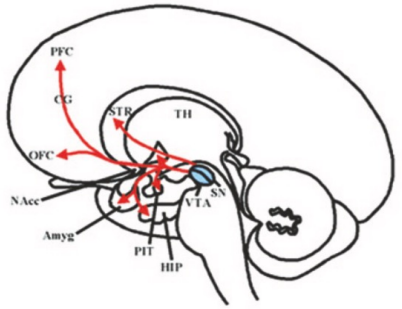
Table 1 Comparison of food and drugs as reinforcers

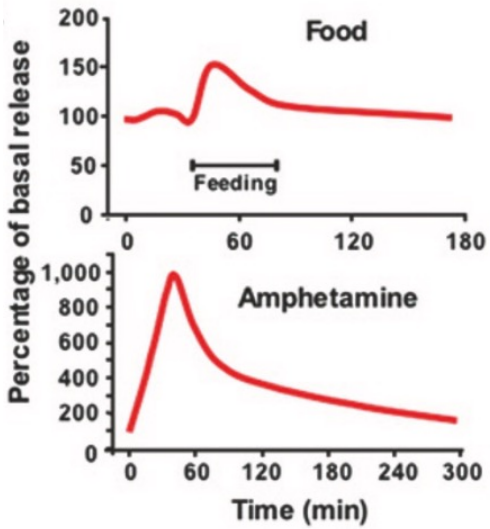
	Food	Drug
Potency as a reinforcer*	++	Oral: ++ Snorted: +++ Smoked, injected: ++++
Delivery	Oral	Oral, snorted, smoked, injected
Mechanism of reward	Somatosensory (palatability), chemical (glucose)	Chemical (drug)
Regulation of intake	Peripheral and central factors	Mostly central factors
Adaptations	Physiologic	Supraphysiologic
Physiological role	Necessary for survival	Unnecessary
Learning	Habits, conditioned responses	Habits, conditioned responses
Role of stress	+++	+++

*Potency as reinforcer is estimated based on the magnitude and duration of increases in dopamine induced by either food or drugs in the nucleus accumbens, and is an approximate comparison, as potency will be a function of the particular foodstuff or of the particular drug and its route of administration.

Volkow & Wise, 2005. *Nat. Neurosc.*

Sistema di ricompensa

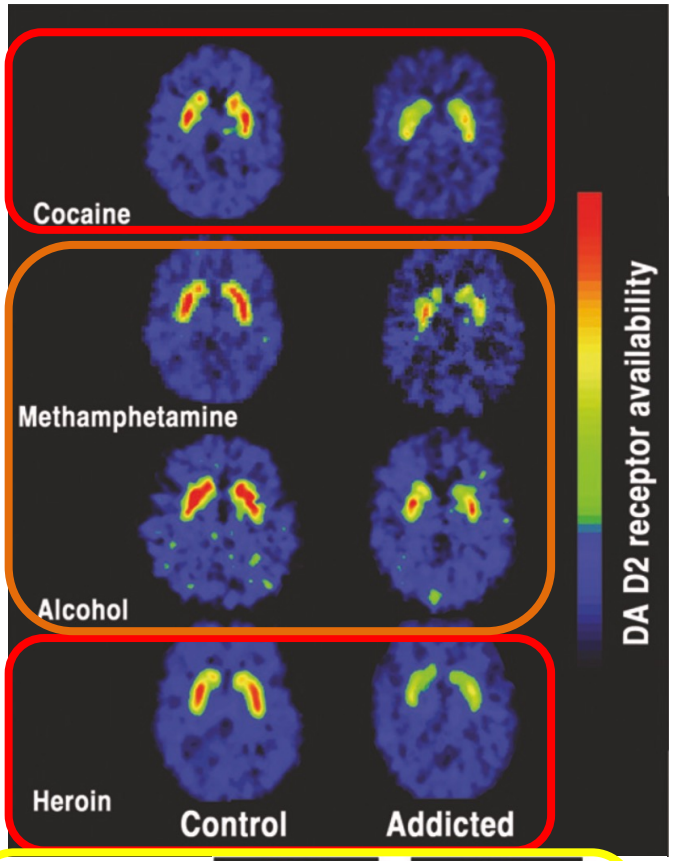


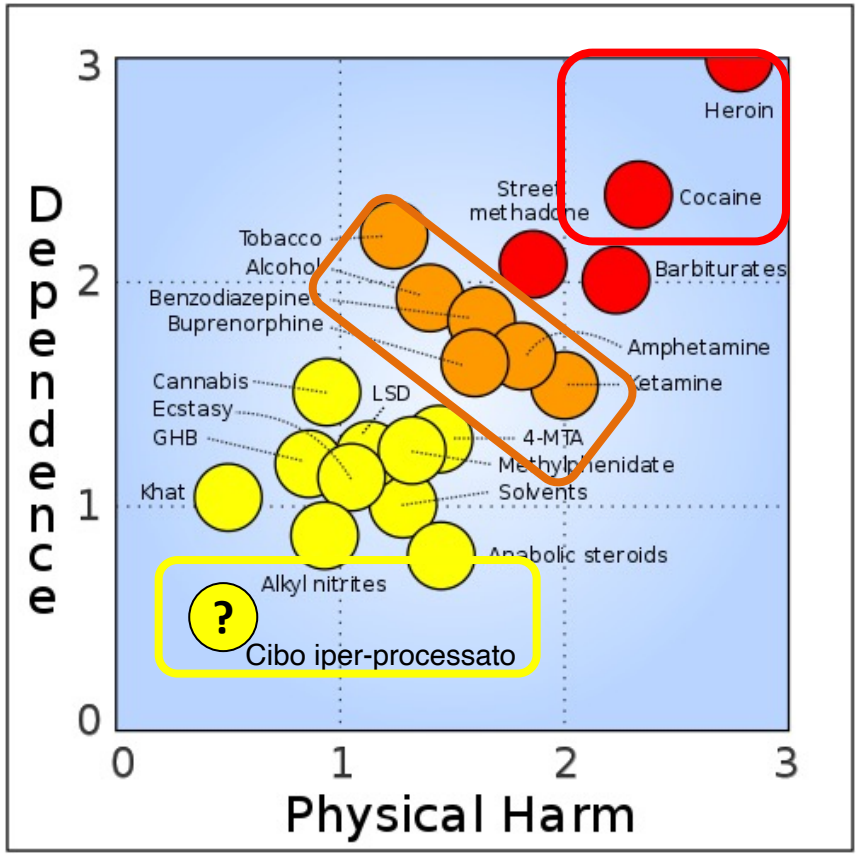


Rilascio di dopamina (DA) nel nucleo accumbens nel topo

Introduzione Generale (ii)

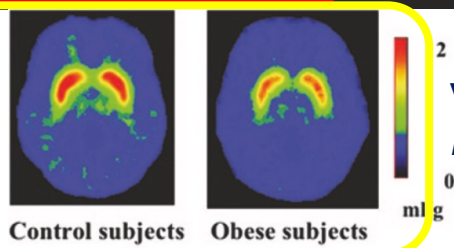
«Abuso» di Cibo Iper-Processato vs. Abuso di Sostanze





Nutt et al., 2007. *The Lancet*

Cibo iper-processato



Volkow & Wise, 2005. *Nat. Neurosc.*

Introduzione

Teorie Neurocognitive dell'Obesità

Hungry brains: A meta-analytical review of brain activation imaging studies on food perception and appetite in obese individuals

F. Devoto[a,b], L. Zapparoli[a], R. Bonandrini[c], M. Berlingeri[d,h], A. Ferrulli[e], L. Luzi[e,g], G. Banfi[a,f], E. Paulesu[a,c,*]

	Eccesso di ricompensa	**Deficit** di ricompensa	**Eccesso** di **anticipazione** di ricompensa > sazietà	**Deficit** di controllo inibitorio
	Reward Surfeit Theory	Reward Deficit Theory	Incentive Sensitization Theory	Inhibitory Control Deficit Theory
Anticipatory Food Cues			**Hyper**-activity of brain regions involved in salience attribution (insula, amygdala, parahippocampal gyrus, hippocampus) and reward (midbrain, striatum, OFC)	**Hypo**-activity of regions involved in inhibitory control (vmPFC, dlPFC)
Consummatory Food Intake	**Hyper**-activity of the reward circuitry (midbrain, striatum, Insula, OFC)	**Hypo**-activity of the reward circuitry (midbrain, striatum, Insula, OFC)		

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Materiali e Metodi (i)

KEYWORDS

Obesity AND :

•fMRI (2935);

•PET (589);

•Functional magnetic resonance imaging (2886);

•Positron emission tomography (453);

•Neuroimaging (645);

Total: 7391 papers

CRITERI DI INCLUSIONE

- Obesi vs. Controlli, Obesi, Controlli
- Adulti
- Stimoli visivi o gustativi
- Digiuno o sazietà dei soggetti
- Analisi whole-brain
- Statistiche univariate
- Compiti attivi
- No somministrazione di farmaci
- Solo dati pre-trattamento

FINAL DATASET

- 22 Studi
- 70 Contrasti
- 650 Foci
- 556 Soggetti

	BMI	ETÀ	DIGIUNO
OBESI	35.5	36.8	8.5 (h)
CONTROLLI	22.3	32.8	

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Materiali e Metodi (ii)

FINAL DATASET

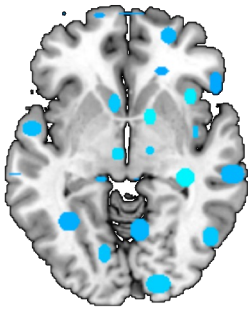
- 650 Activation Foci

FOCI CLASSIFICATION

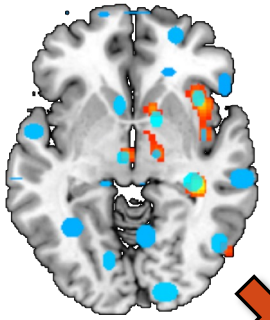
- **GRUPPO** — OBESI / CONTROLLI
- **MODALITÀ** — VISIVA / GUSTATIVA
- **SAZIETÀ** — DIGIUNO / SAZIO

HIERARCHICAL CLUSTERING ANALYSIS

CluB

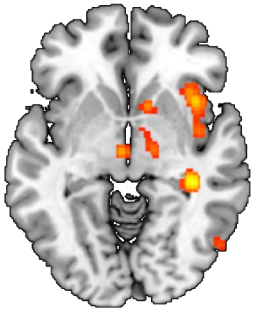


5 mm



Ginger ALE

ACTIVATION LIKELIHOOD ESTIMATION



p < 05 FDR

CLUSTER COMPOSITION ANALYSIS

EFFETTI PRINCIPALI

Test Binomiali

INTERAZIONI

Test di FIsher

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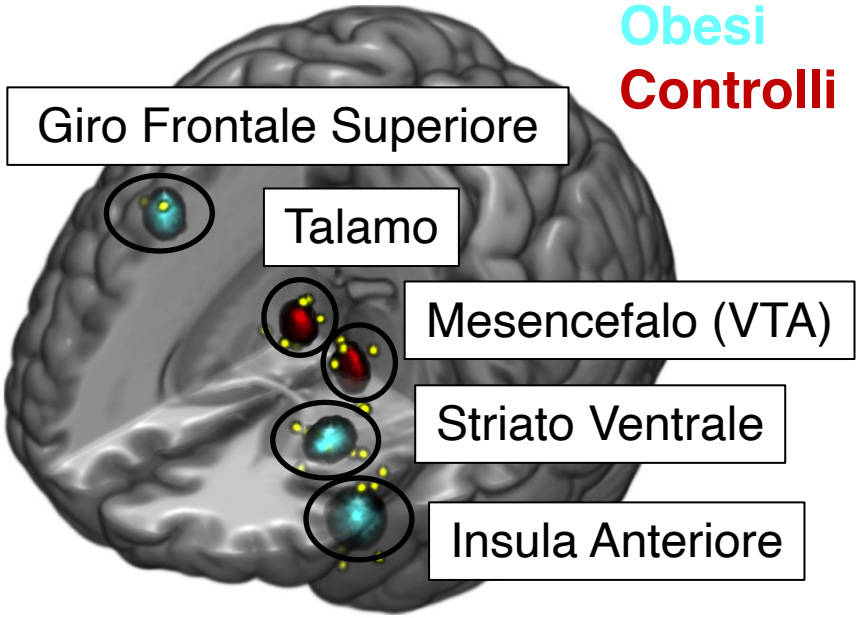
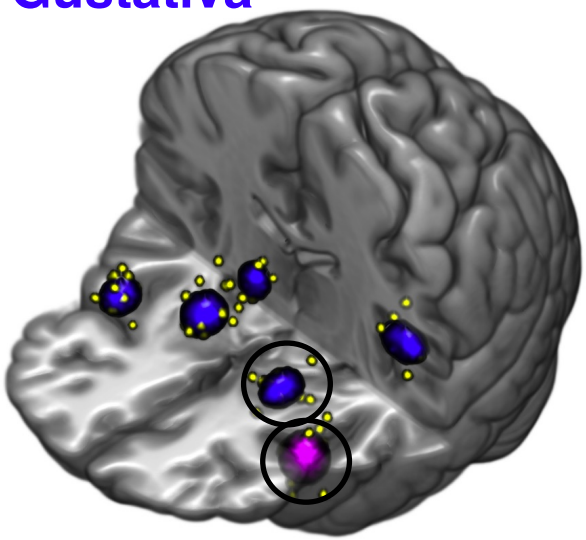
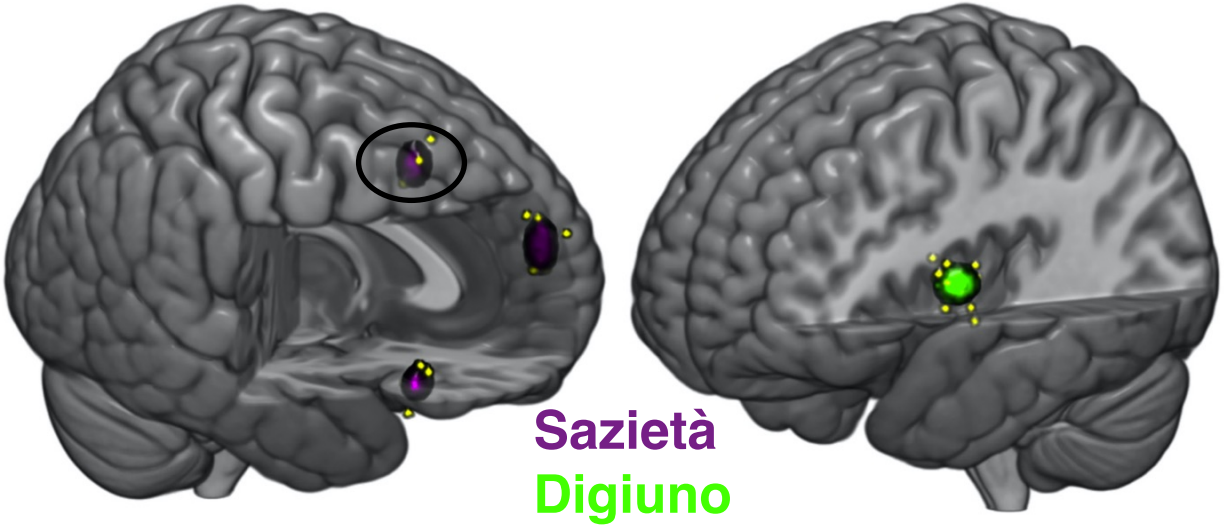
Risultati (i)







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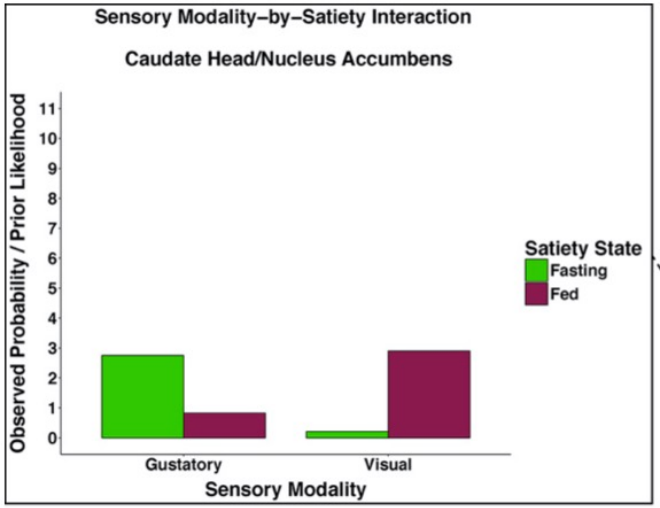
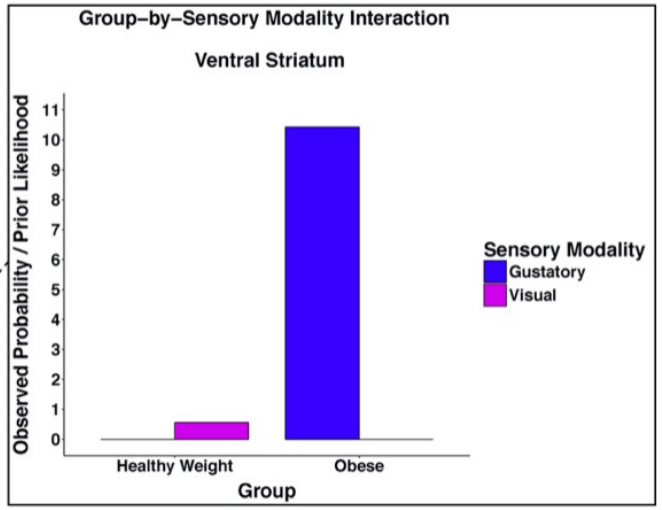
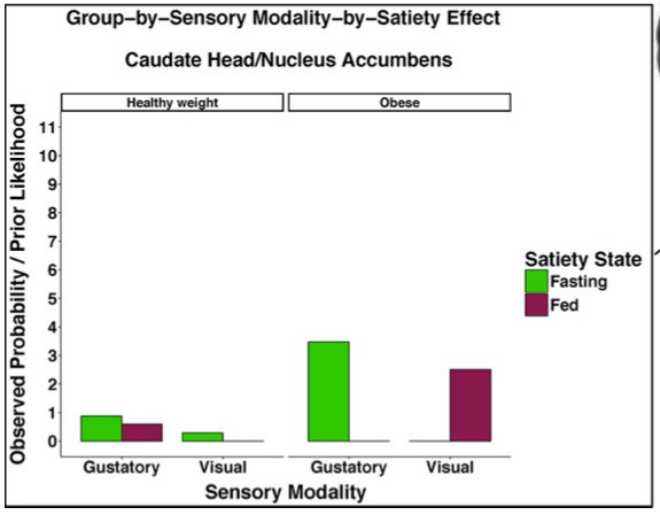
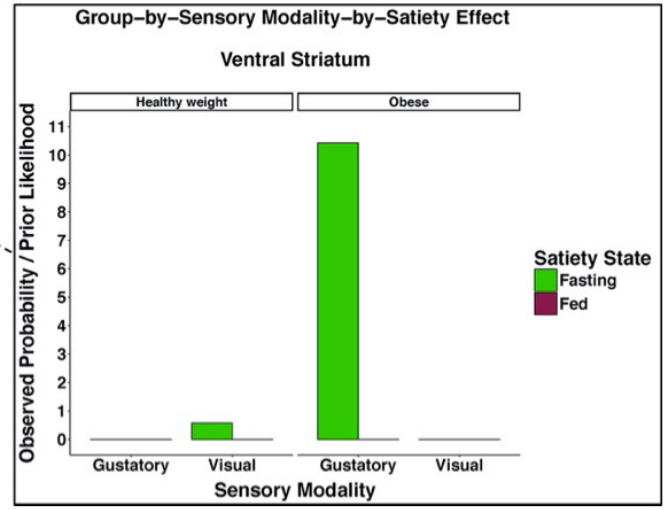
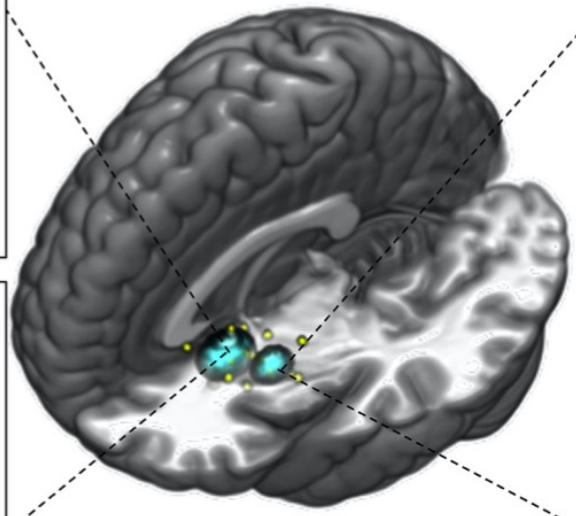
Risultati (ii)











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Discussione

1. L'obesità è associata ad **alterate risposte neurofunzionali** al cibo, in aree corticali e sottocorticali coinvolte nei processi edonici e motivazionali.

	Reward Surfeit Theory	Reward Deficit Theory	Incentive Sensitization Theory	Inhibitory Control Deficit Theory
Anticipatory Food Cues			**Hyper**-activity of brain regions involved in salience attribution (insula, amygdala, parahippocampal gyrus, hippocampus) and reward (midbrain, striatum, OFC)	**Hypo**-activity of regions involved in inhibitory control (vmPFC, dlPFC)
Consummatory Food Intake	**Hyper**-activity of the reward circuitry (midbrain, striatum, Insula, OFC)	**Hypo**-activity of the reward circuitry (midbrain, striatum, Insula, OFC)		

2. La **Reward Surfeit Theory** e la **Incentive Sensitization Theory** hanno ricevuto il maggiore supporto dai dati neurofunzionali.

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Introduzione

Alterazioni Neurostrutturali nell'Obesità

Neural structural abnormalities behind altered brain activation in obesity: Evidence from meta-analyses of brain activation and morphometric data

Laura Zapparoli [a,b,1,*], Francantonio Devoto [a,1], Gianluigi Giannini [a], Sara Zonca [a], Francesca Gallo [a], Eraldo Paulesu [a,b]

[a] *Psychology Department and NeuroMi – Milan Centre for Neuroscience, University of Milano-Bicocca, Milan, Italy*
[b] *IRCCS Orthopedic Institute Galeazzi, Milan, Italy*

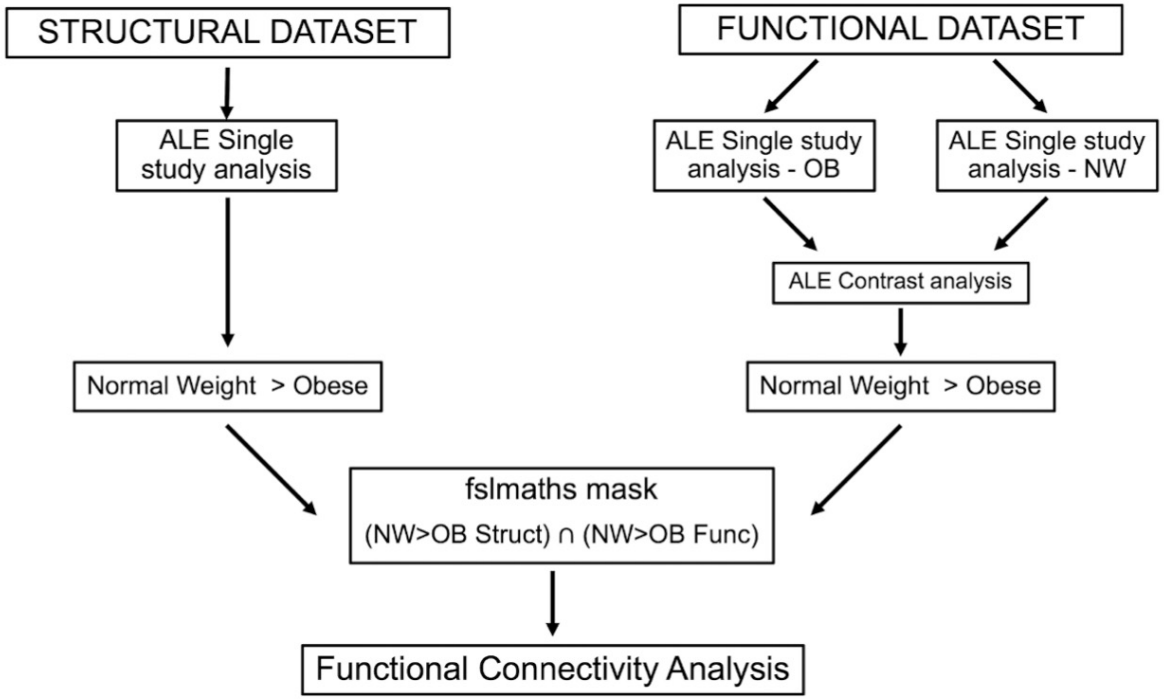
1. Le **alterazioni morfometriche** rilevate nell'obesità convergono spazialmente a livello meta-analitico e in **quali circuiti cerebrali**?

2. Esiste una **sovrapposizione anatomica** fra le alterazioni **funzionali** e **strutturali** associate all'obesità?

Materiali e Metodi

Meta-analisi di studi morfometrici

- Studi voxel-based morphometry (VBM) o correlazioni con body mass index (BMI)
- 27 articoli inclusi
- 570 foci (Normopeso > Obesità)
- Oltre 7000 partecipanti



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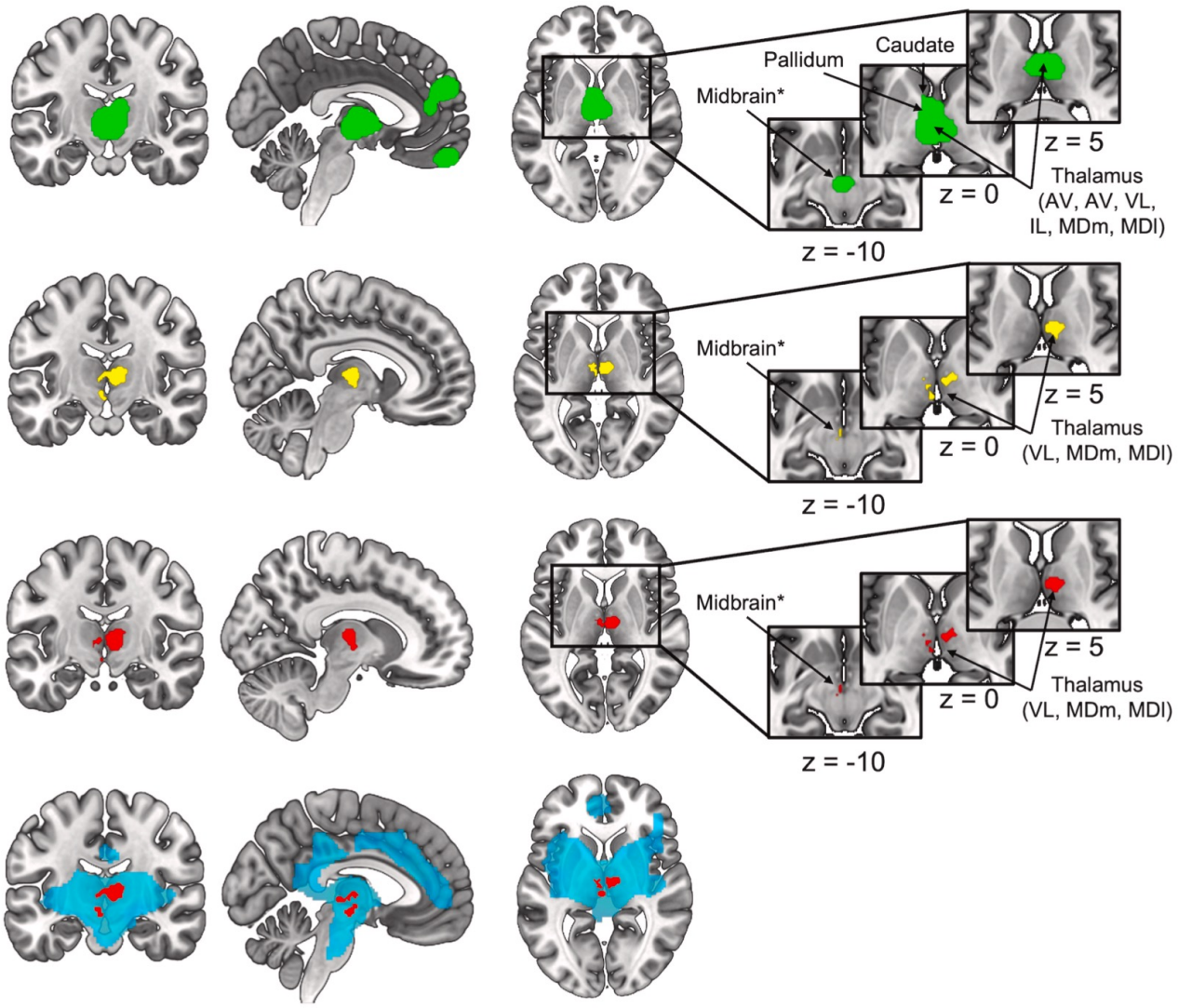
Risultati

Ipo-densità di materia grigia in pazienti obesi

Ipo-attivazione in risposta al cibo in pazienti obesi

Sovrapposizione anatomica fra le due mappe

Connettività funzionale a riposo in soggetti normopeso



Discussione

Convergenza anatomica fra alterazioni funzionali e strutturali

1. L'obesità è associata ad una **riduzione di densità di materia grigia** nel **talamo**, **mesencefalo** e **corteccia prefrontale**.

2. Esiste una **convergenza anatomica fra le alterazioni funzionali e strutturali** associate all'obesità, in regioni talamiche e mesencefaliche.

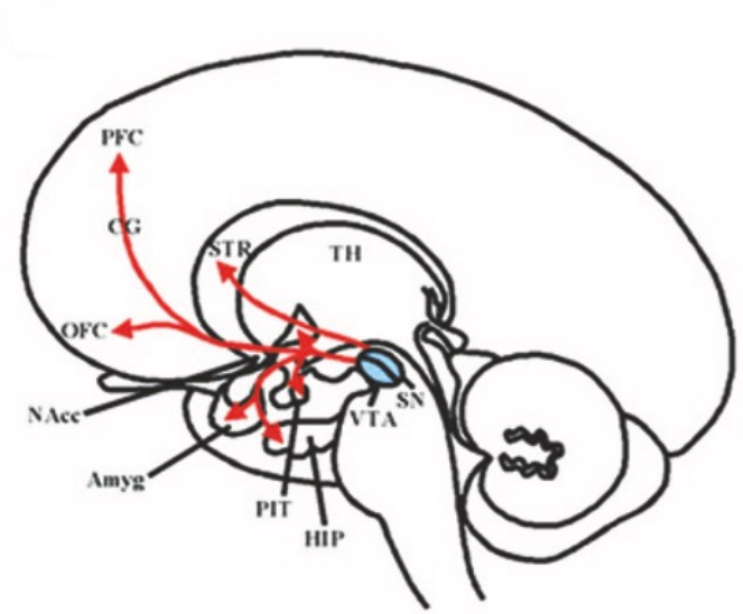
Introduzione

How images of food become cravingly salient in obesity

Francantonio Devoto [1] | Anna Ferrulli [2,3] | Giuseppe Banfi [4,5] | Livio Luzi [2,3] | Laura Zapparoli [1,4] | Eraldo Paulesu [1,4]

- L'obesità è associata ad una **alterata connettività funzionale** dei nuclei dopaminergici dell'Area Tegmentale Ventrale (VTA)?

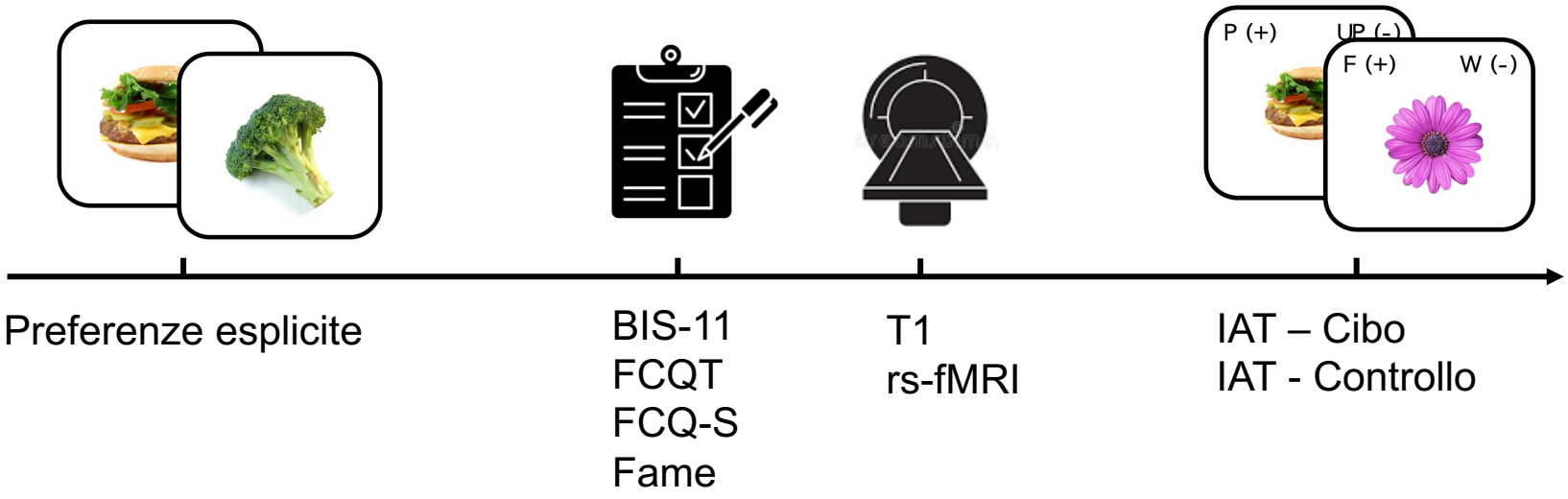
MOTIVAZIONE



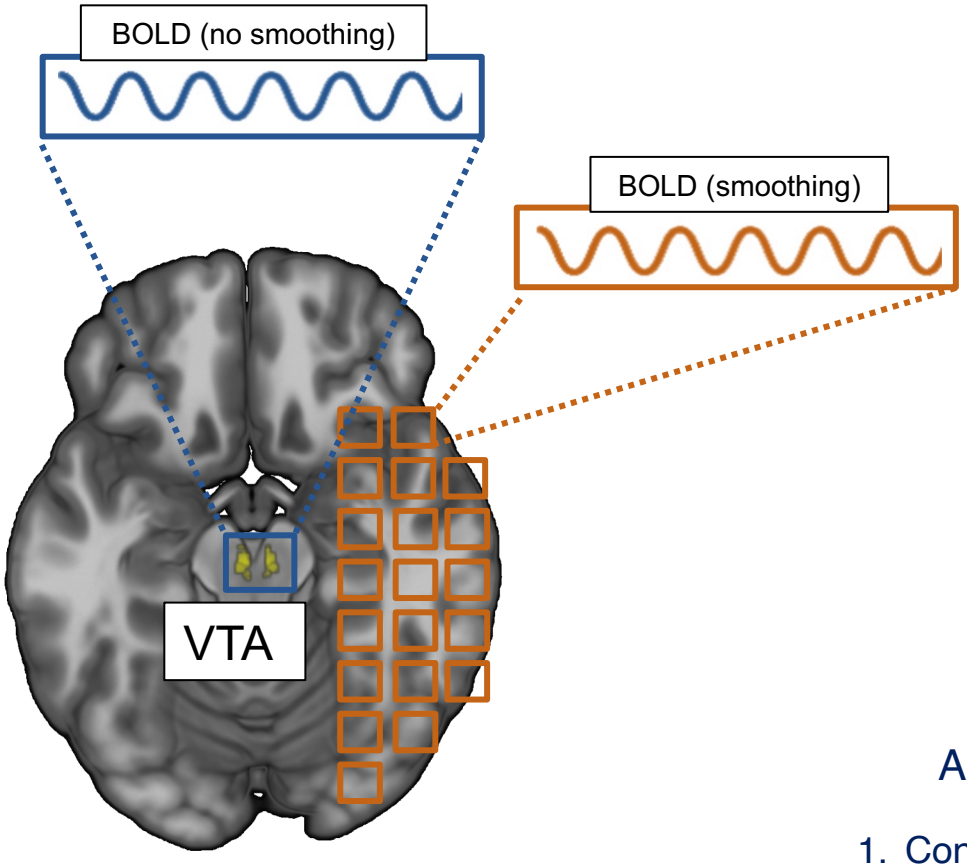
CONTROLLO

Metodi (i)

	Normopeso (n = 23)	Obesi (n = 23)	
	Media (DS)	Media (DS)	
Genere (M/F)	7/16	6/17	$\chi^2 = 0.11$, $p = 0.74$
Età	46 (11.5)	51.4 (9.3)	$U = 186$, $p = 0.08$
Istruzione	14.9 (3)	14 (3.2)	$U = 225$, $p = 0.37$
BMI (kg/m^2)	23.2 (1.5)	36 (3.5)	$t(44) = -16.19$, $p < 0.001$
Digiuno (minuti)	252 (40.5)	300.6 (132.4)	$U = 187$, $p = 0.09$



Metodi (ii)



- VTA bilaterale
- AAL3 Template (Rolls et al. 2020)

ACQUISIZIONE

- Immagine strutturale (T1)
- Funzionale BOLD (350 scan resting-state)

PREPROCESSING

- Slice-timing correction
- Riallineamento a prima immagine funzionale
- Segmentazione T1
- Coregistrazione
- Normalizzazione
- Smoothing (10mm)

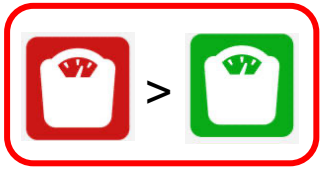
DENOISING

- Filtro band-pass (.008-.09 Hz)
- Drift lineare del segnale
- Regressione segnale WM e CSF (CompCor)
- Regressione movimento (rigid body 6 + scrubbing)

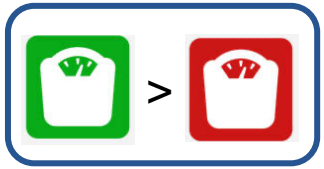
ANALISI DI GRUPPO

1. Connettività media della VTA

2. **Iper-connettività** nei pazienti

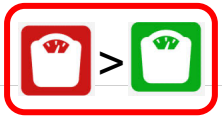


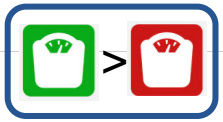
3. **Ipo-connettività** nei pazienti



Risultati (i)

PAZIENTI vs. CONTROLLI





R

FFG

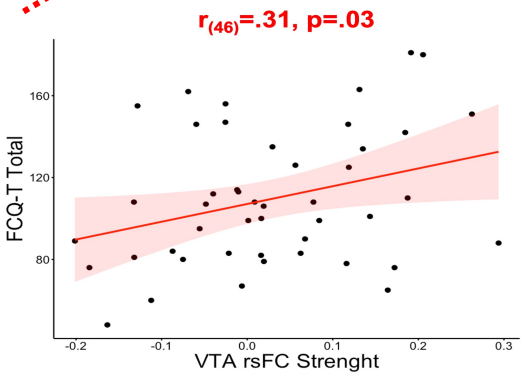
L

$p < .05$,
cluster-level FWE

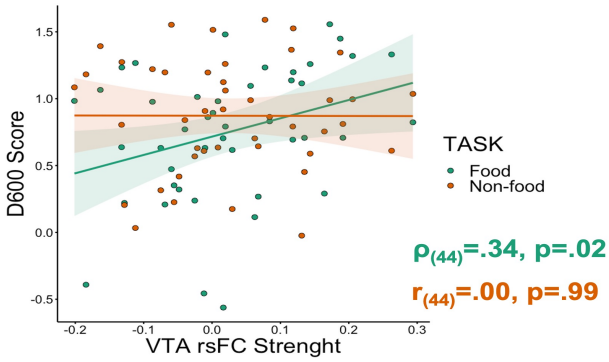
A

IFG

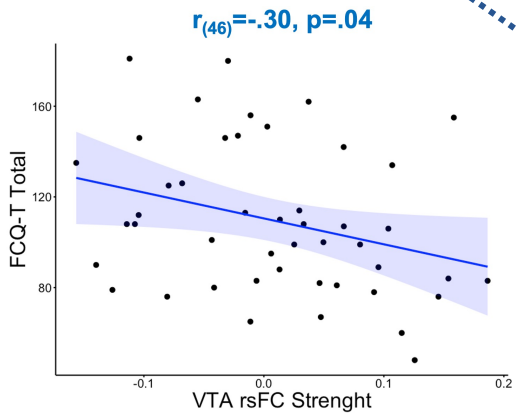
P



FOOD CRAVING



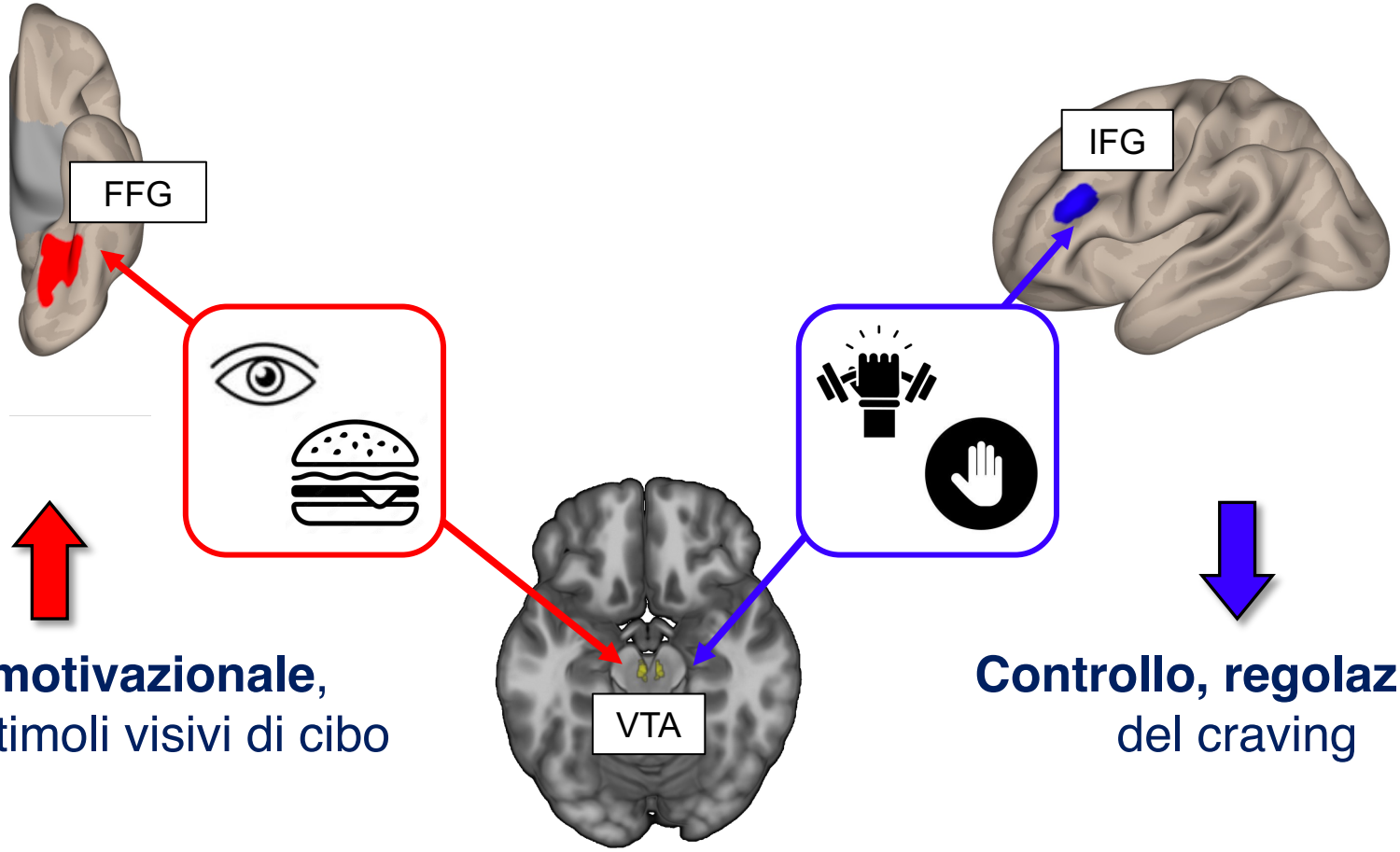
BIAS IMPLICITO



FOOD CRAVING

Discussione

L'obesità è associata a **pattern di connettività funzionale alterati** della VTA.



Valore motivazionale, **salienza** stimoli visivi di cibo

Controllo, regolazione del craving

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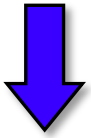
Introduzione (i)

Repetitive deep TMS for the reduction of body weight: Bimodal effect on the functional brain connectivity in "diabesity"

Francantonio Devoto [a,1], Anna Ferrulli [b,c,1], Laura Zapparoli [d], Stefano Massarini [c], Giuseppe Banfi [e], Eraldo Paulesu [d,e], Livio Luzi [b,c,*]

APPROCCI DI INTERVENTO «BRAIN-CENTERED»



MOTIVAZIONE, SALIENZA

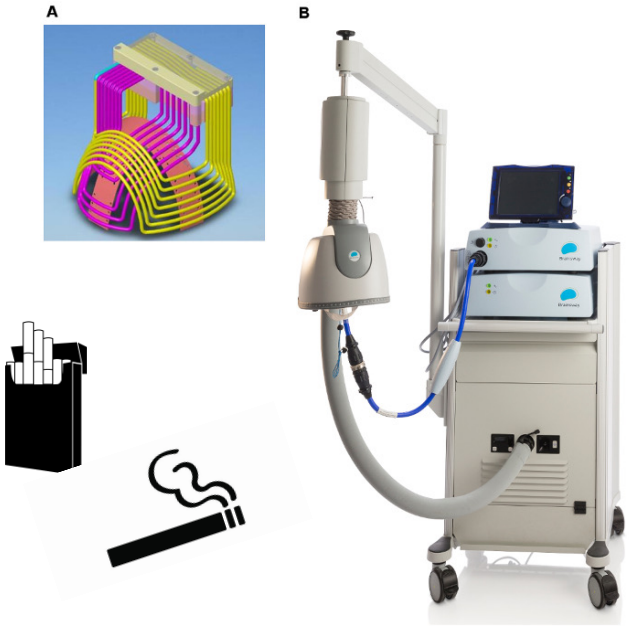
INIBIZIONE, REGOLAZIONE

Introduzione (ii)

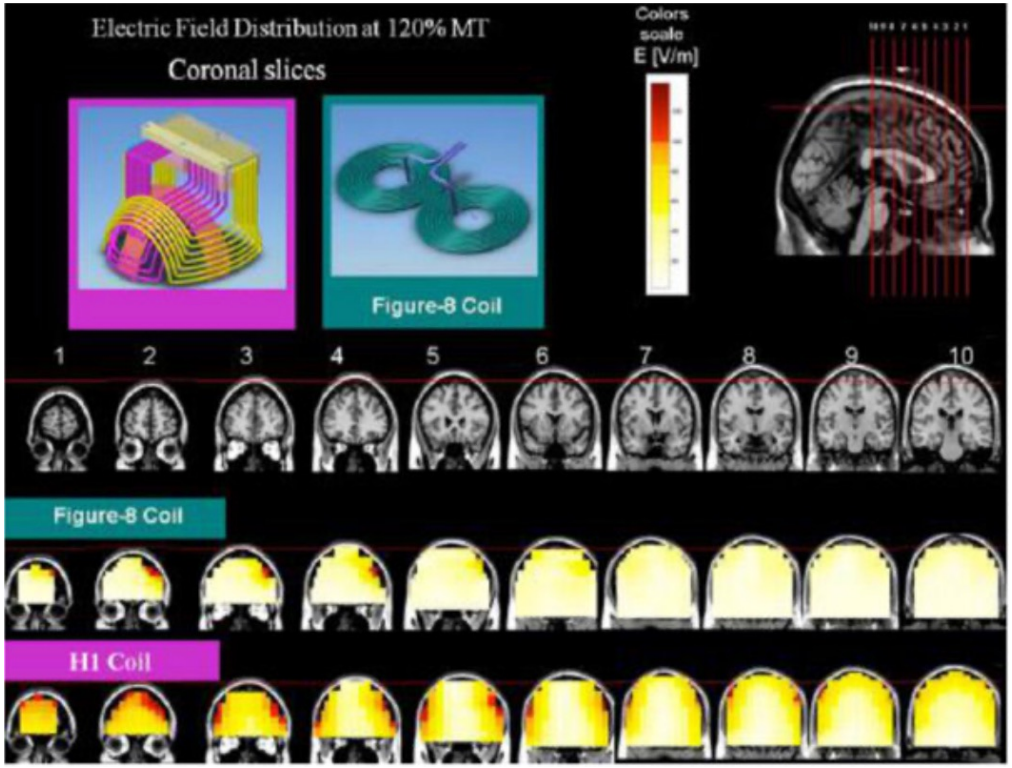
ARCHIVAL REPORT

Smoking Cessation Induced by Deep Repetitive Transcranial Magnetic Stimulation of the Prefrontal and Insular Cortices: A Prospective, Randomized Controlled Trial

Limor Dinur-Klein, Pinhas Dannon, Aviad Hadar, Oded Rosenberg, Yiftach Roth, Moshe Kotler, and Abraham Zangen

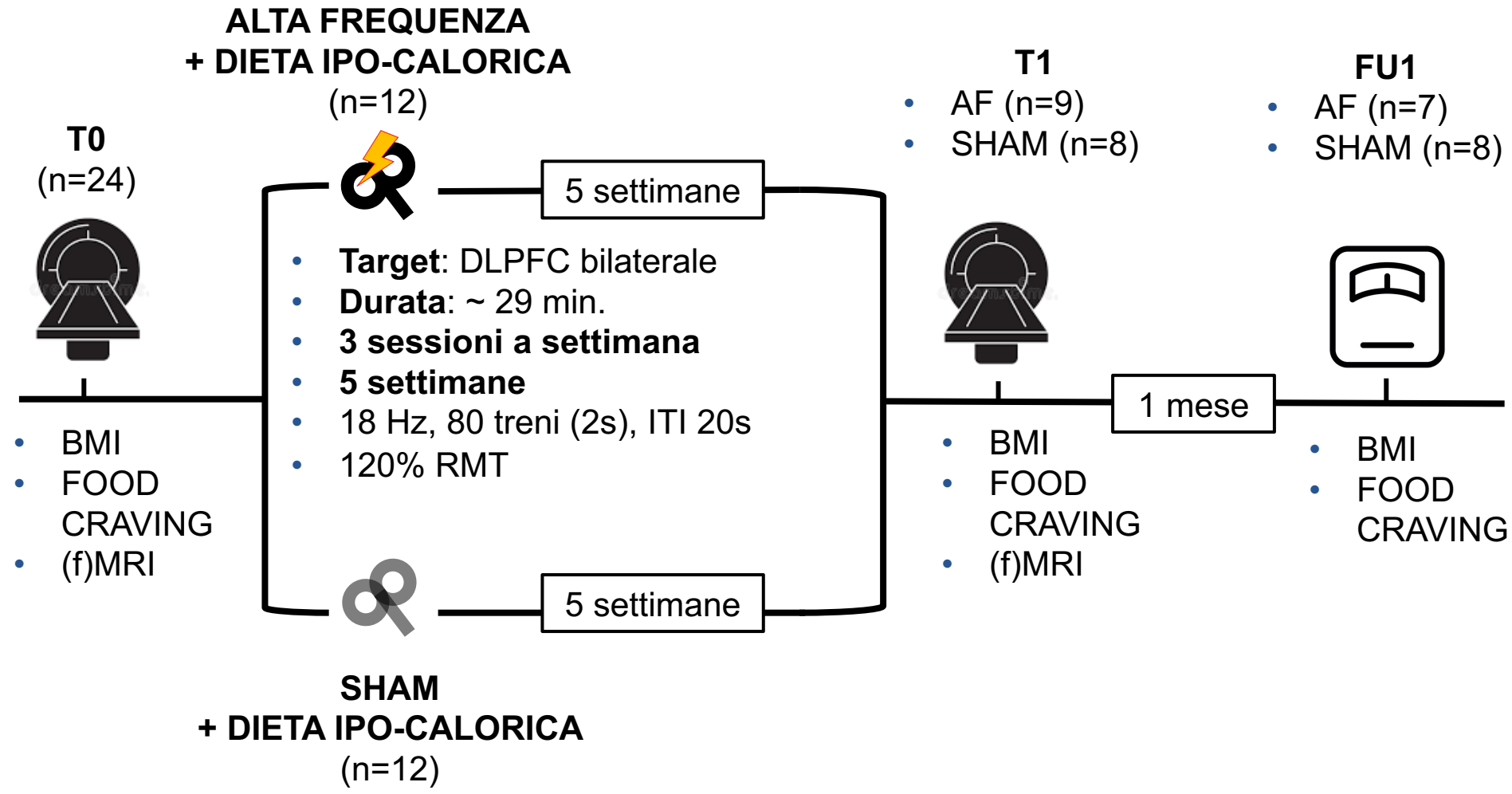


Tendler et al. 2017



Feifel and Pappas, 2016

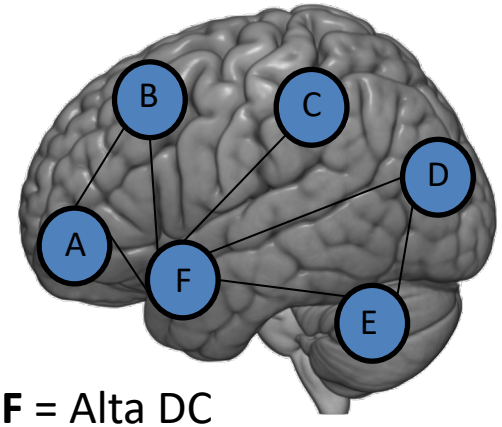
Materiali e Metodi (i)



Materiali e Metodi (ii)

La Degree Centrality (DC) è una misura di **integrazione funzionale =** misura il grado in cui una regione (voxel) è funzionalmente connessa con il resto (dei voxel) del cervello.

C = Bassa DC



F = Alta DC

EFFETTO DEL TRATTAMENTO (DC)

In quali aree il trattamento induce cambiamenti nelle proprietà di integrazione funzionale?

CONNETTIVITÀ FUNZIONALE (T0)

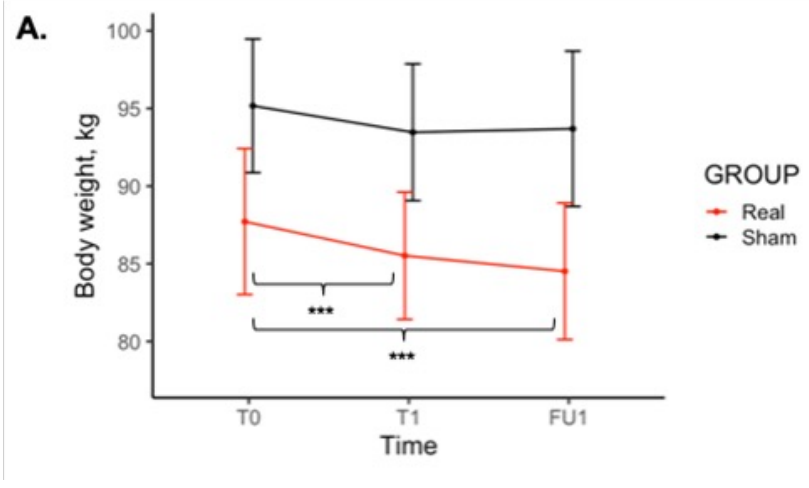
A quali circuiti cerebrali sono funzionalmente connesse?

COGNITIVE DECODING (NeuroSynth)

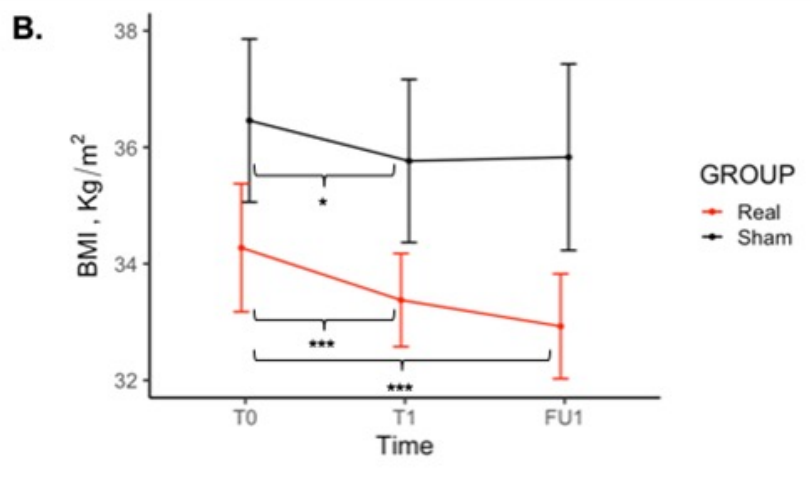
A quali domini cognitivi sono associati questi circuiti?

Risultati (i)

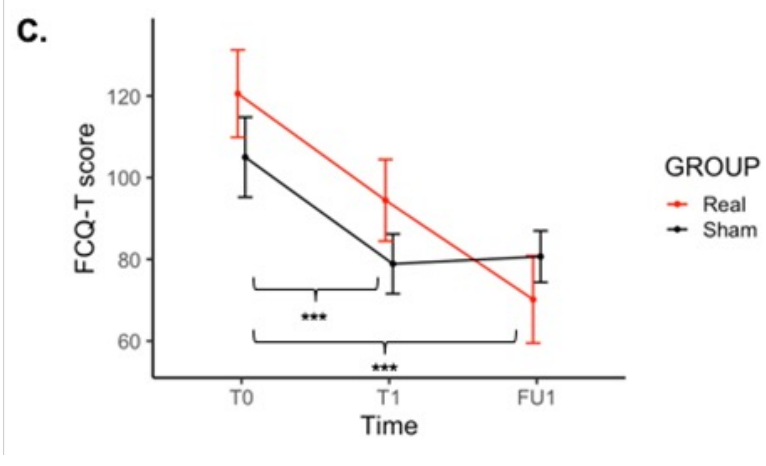
PESO (kg)



BMI (kg/m^2)



FOOD CRAVING



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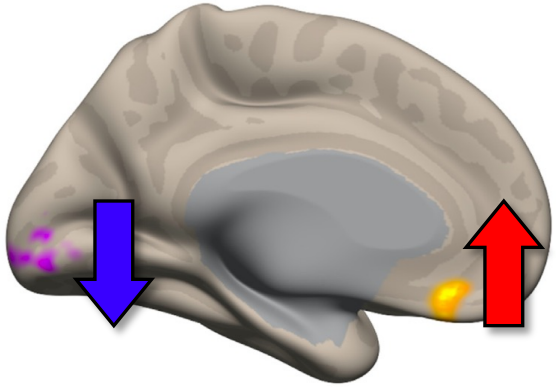
Risultati (ii)

DEGREE CENTRALITY

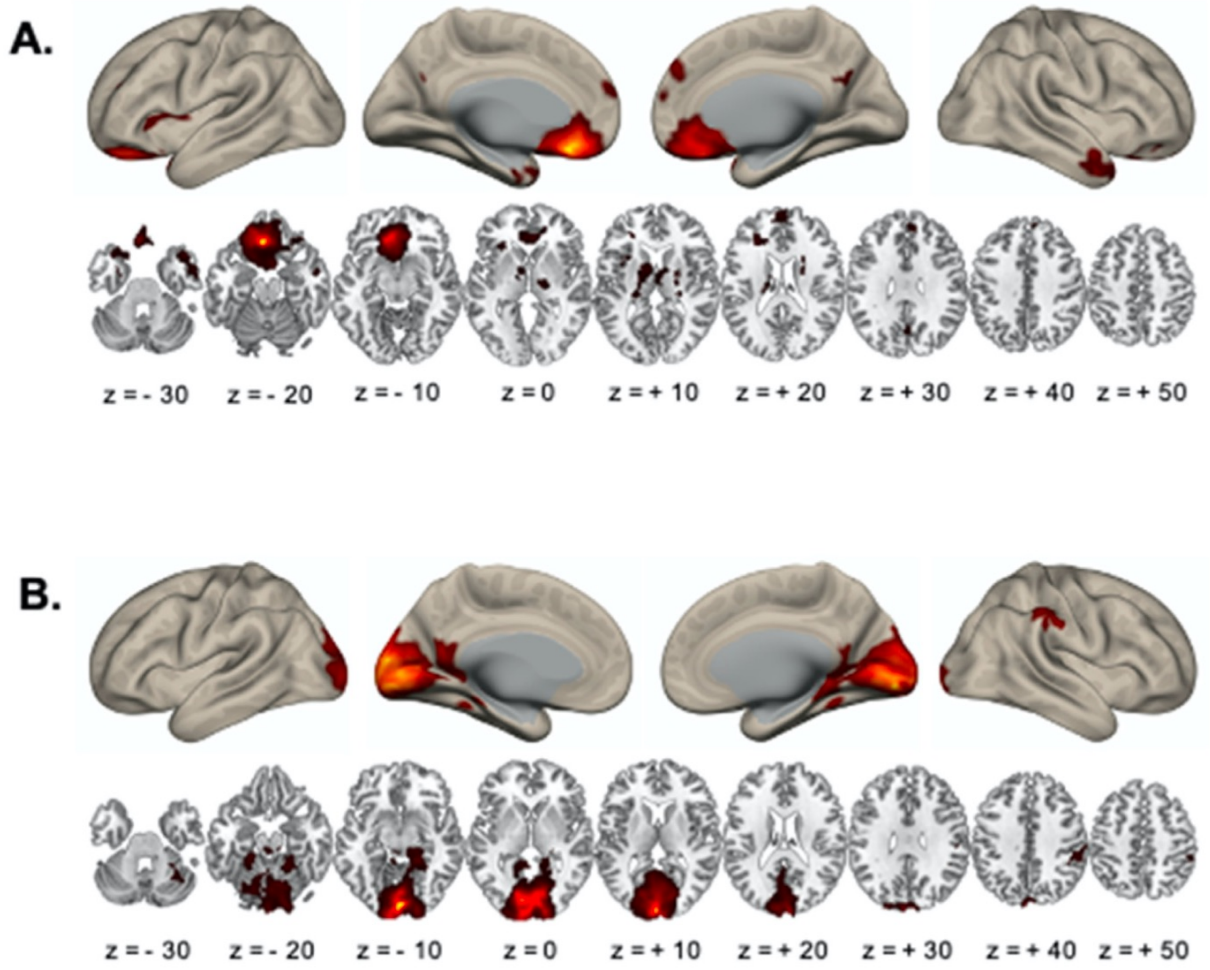


realTMS > shamTMS [T0 > T1]

realTMS > shamTMS [T0 < T1]

p < .05,
cluster-level FWE

CONNETTIVITÀ FUNZIONALE



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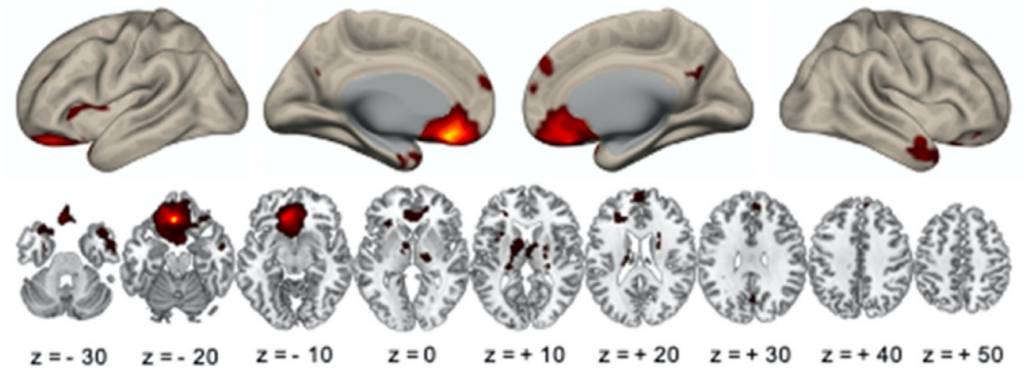
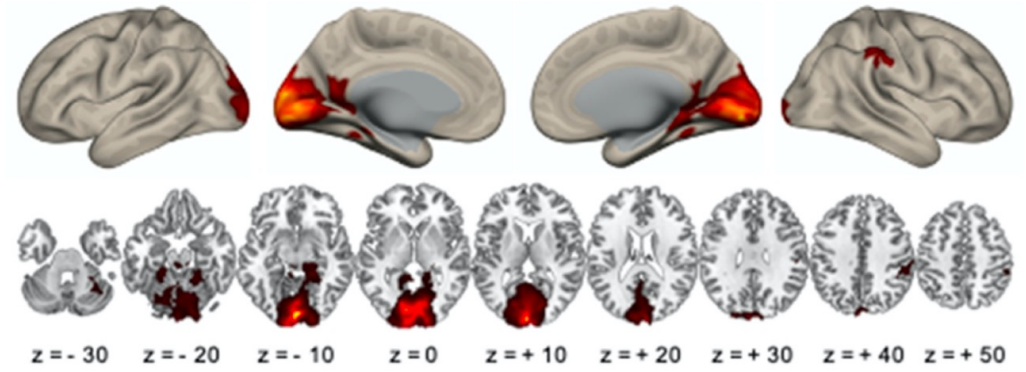
Risultati (iii)

DECODIFICA COGNITIVA DELLE MAPPE DI CONNETTIVITÀ FUNZIONALE

A.

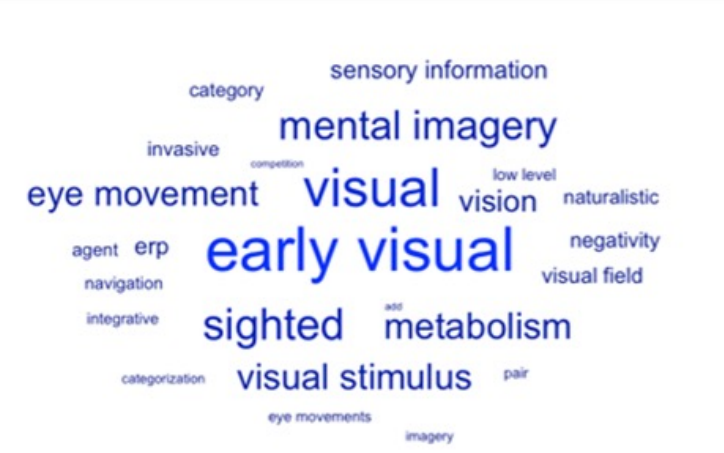


B.



A.

B.



Conclusioni

L'obesità è associata ad alterazioni cerebrali in termini di:

1. Risposte neurofunzionali a stimoli di cibo: ↑ reward/motivation
2. Riduzioni di densità di materia grigia: ↓ inhibition/decision-making
3. Connettività funzionale a riposo: reward/motivation ↔ inhibition/decision-making

Neural circuits mediating food cue-reactivity: Toward a new model shaping the interplay of internal and external factors

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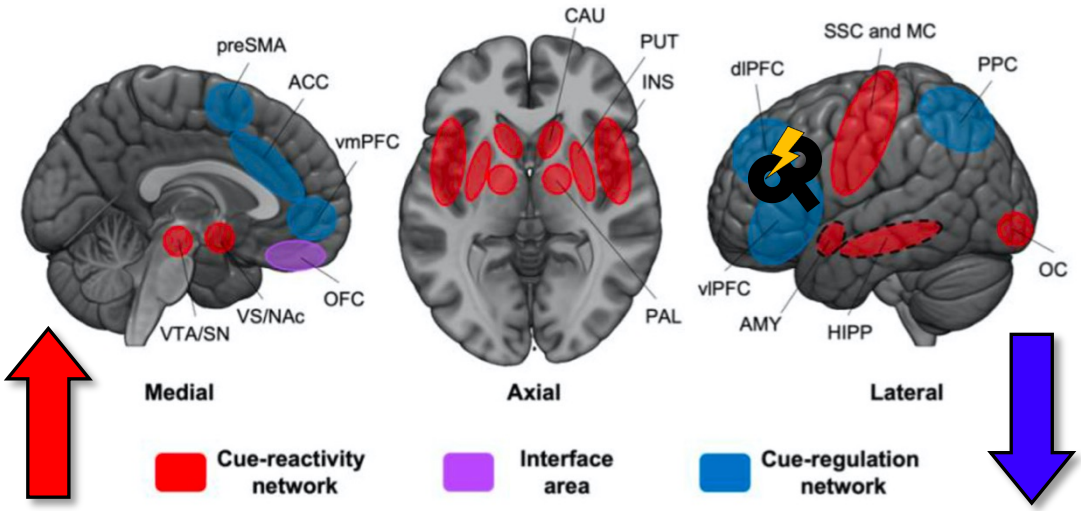

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Ringraziamenti

Grazie per l'attenzione!

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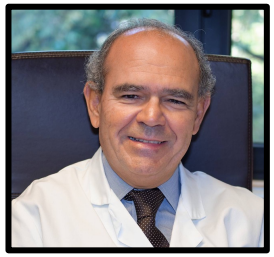
Dipartimento di Psicologia
Università di Milano-Bicocca



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