Addiction Therapy-2014

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Igor Elman

NEUROIMAGING OF REWARD DEFICIENCY SYNDROME: CHRONIC STRESS AND BEHAVIORAL ADDICTION FINDINGS

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August 4, 2014

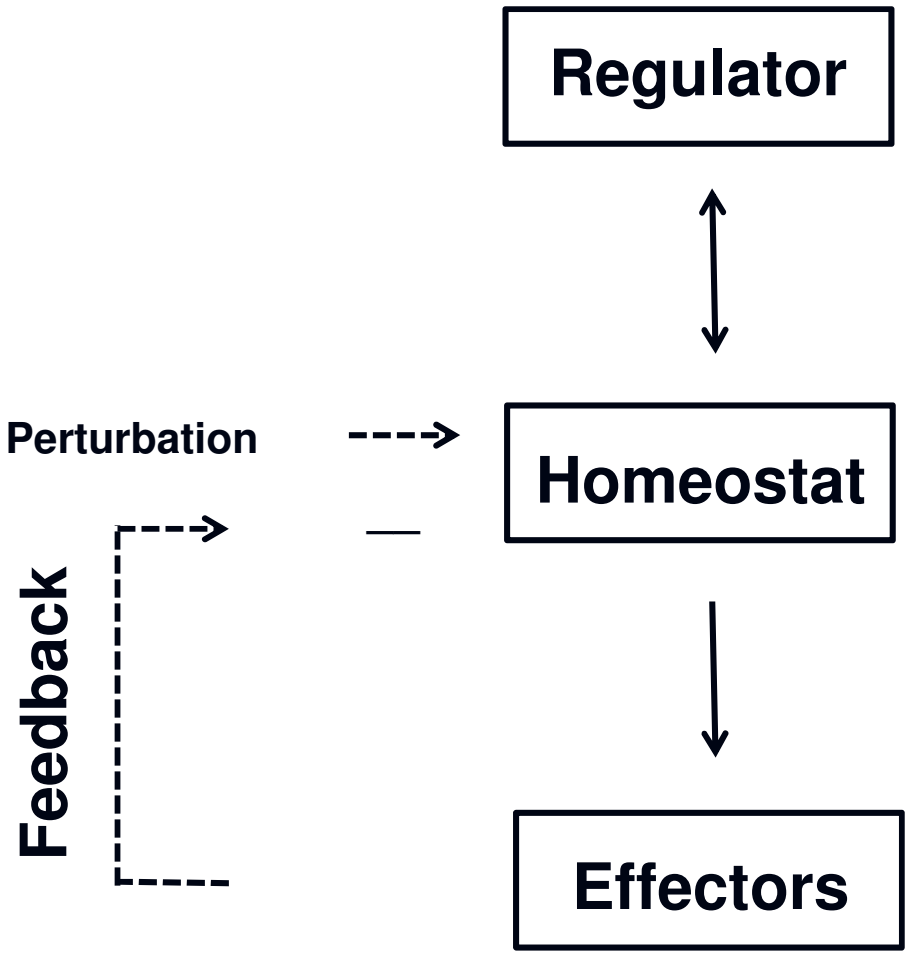
Outline

- Definition
  - reward
  - reward deficiency
- Data
  - PTSD
  - GD
  - SUDs

REWARD

- Rodent, primate models & human neuroimaging
  - mesoaccumbens dopamine pathway
  - VTA (midbrain) → NAc (forebrain)
- Mediates pleasure, contentment & motivation
- ↑ DA common element; nature is being debated
- Homeostasis
  - Regulators: determine set point for responding
  - Homeostat ("Rewardstat?"): compare information
  - Effector systems: change values of controlled variable

HOMEOSTATIC SYSTEM OF REWARD



Anatomic

-PFC
-Amygdala
-Hypothalamus
-Habenula
-Insula

-VT
-NAc

Neurochemical

-Opioids
-Glutamate
-GABA
-Serotonine
-Cannabinoids
-NE
-ACh

DA

-Postsynaptic DA receptors
-DA synthesis & release
-DA transporters

REWARD DEFICIENCY

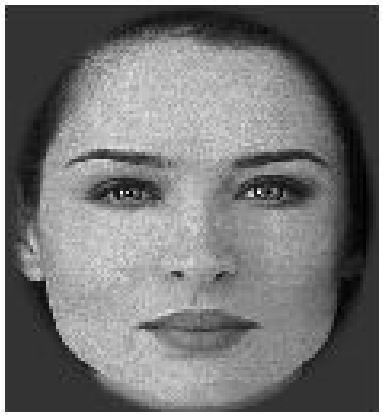
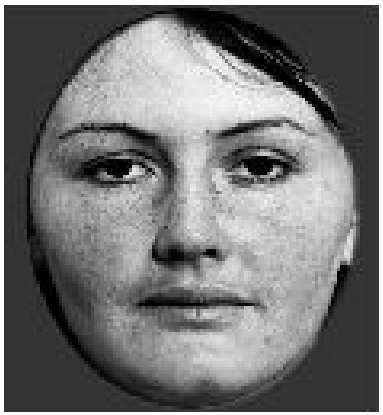
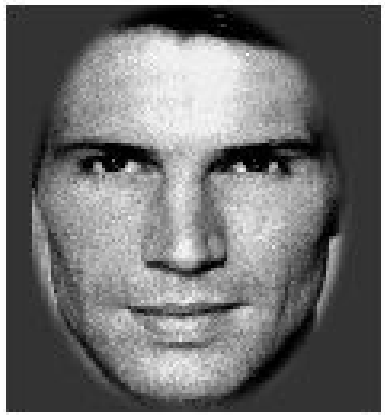
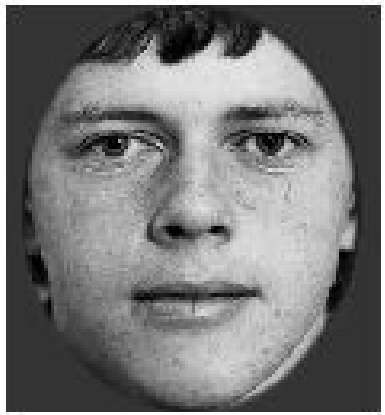
- ↑↑↑ DA → dysfunctional ↓DA state
- ↓ Responsivity to natural reinforcers
  - SUDs: clinical impression
    - exogenous neurotoxicity
    - sensitization, cross-sensitization & anti-reward
  - ~ COPD
    - ↓ in sensitivity to CO_2
    - ↑ in sensitivity to O_2

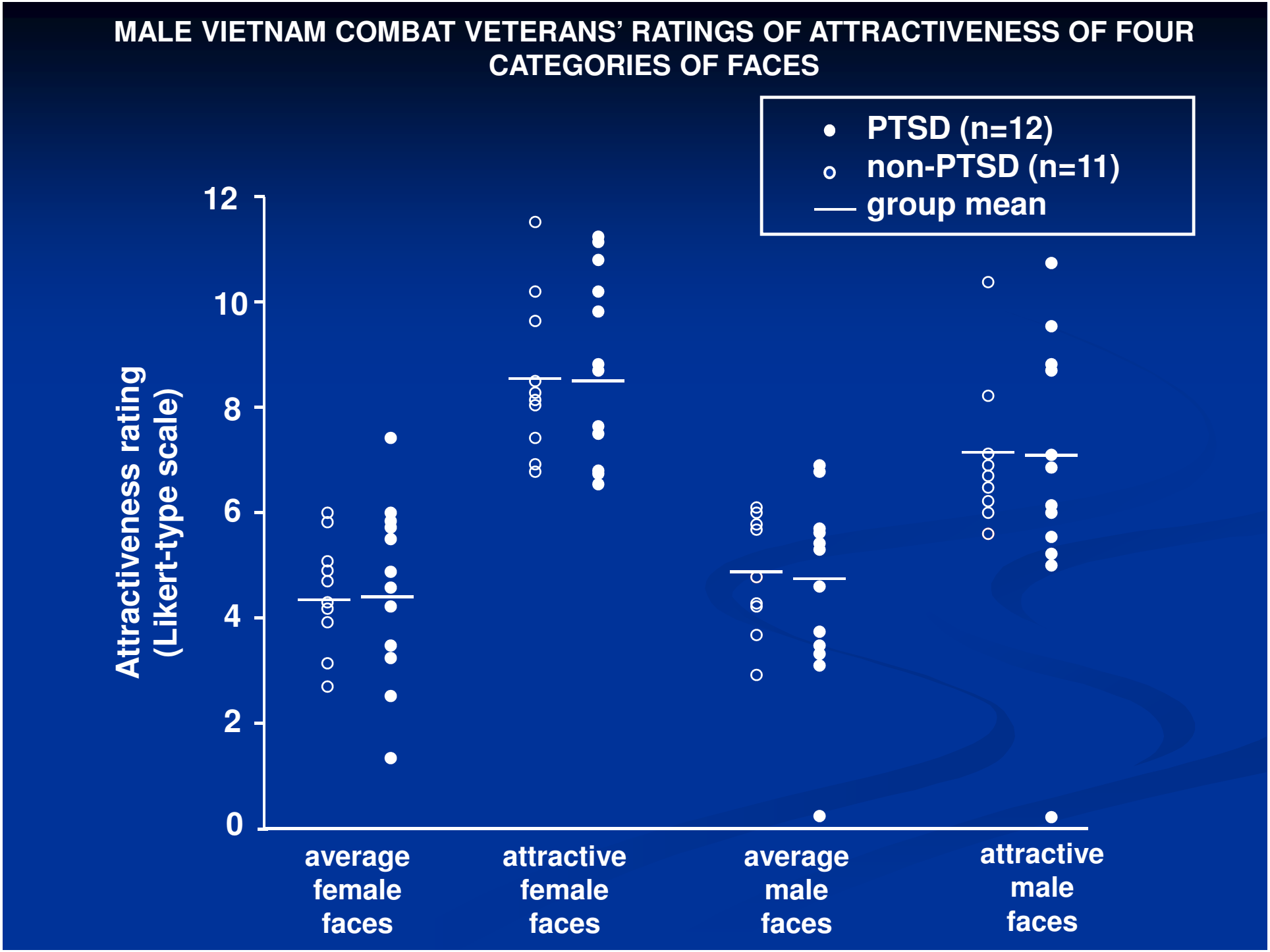
REWARD DEFICIENCY & PTSD

- Preclinical studies
  - acute stress → ↑DA neurotransmission
  - chronic stress → ↓ DA neurotransmission
  - ↓ motivation towards pleasurable stimuli

KEY PRESS TASK

- Offline tasks
  - prior neuroimaging
  - key press (press various keys to change viewing time)
    - alternating “z” & “x” keys decrease viewing time (up to 4 sec); the “n” & “m” keys increase time (up to 12 sec)
    - measure of interest: # of key presses
  - rating task
    - measure of facial attractiveness: scale: 0-100, 0 is “very unattractive” and 100 is “very attractive”


MALE VIETNAM COMBAT VETERANS' RATINGS OF ATTRACTIVENESS OF FOUR CATEGORIES OF FACES
PTSD (n=12)
non-PTSD (n=11)
group mean
Attractiveness rating (Likert-type scale)
12
10
8
6
4
2
0
average female faces
attractive female faces
average male faces
attractive male faces

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Probing reward function in post-traumatic stress disorder with beautiful facial images

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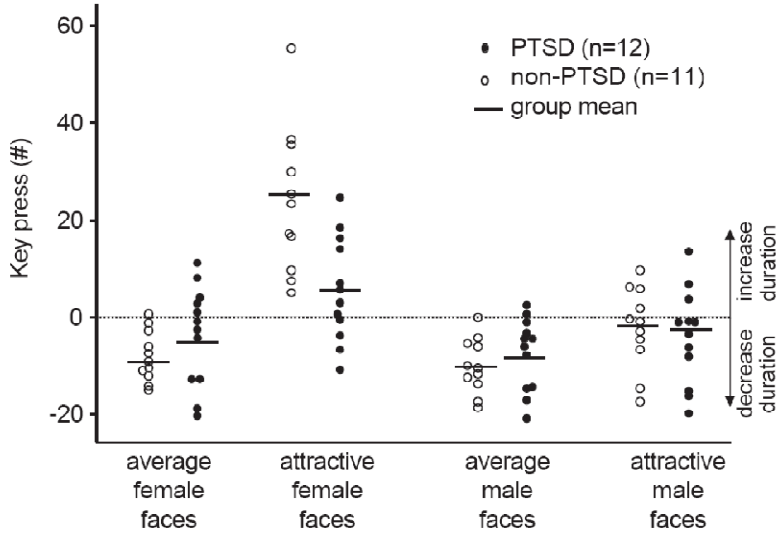
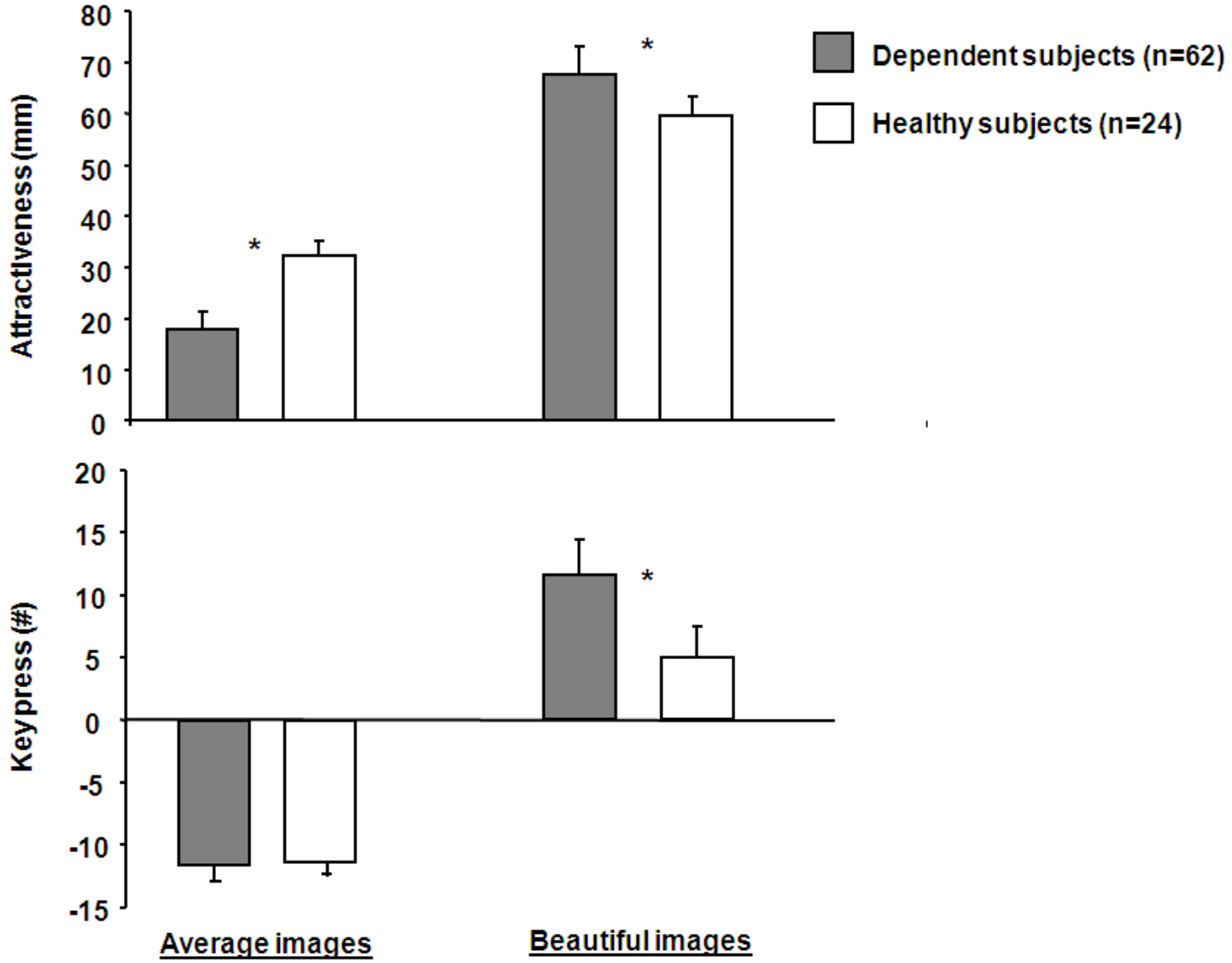


Fig. 1. Male Vietnam combat veterans' efforts to increase or decrease viewing times of four categories of faces (values represent a subject's net key presses, as defined in the text).

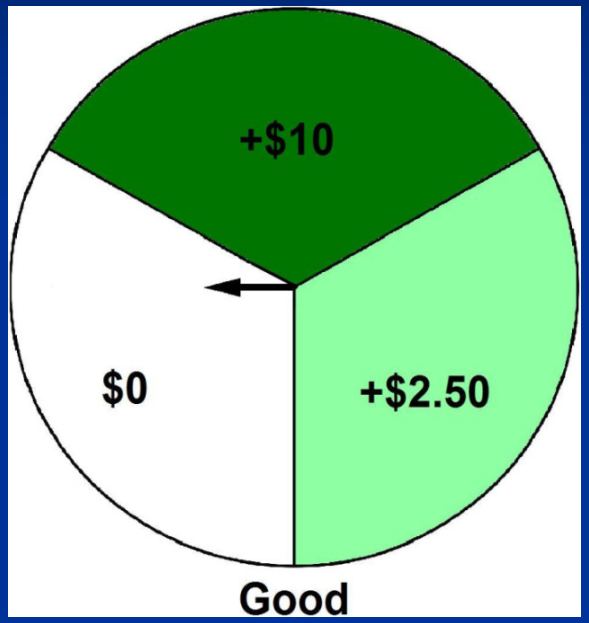
ALCOHOL, OPIOID AND COMORBID DEPENDENCE

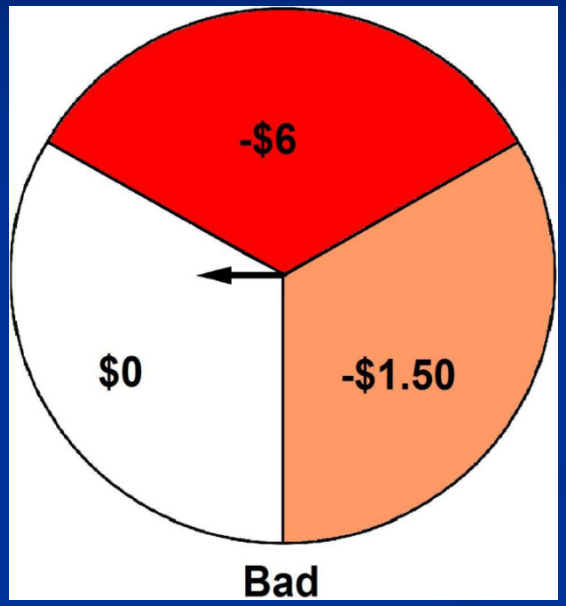
- Fully detoxified male heterosexual participants
  - alcohol dependence (N=20; age ± SD: 33.7±4.64)
  - heroin dependence (N=18; 28.1±4.69)
  - comorbid alcohol/heroin dependence (N=22; 27.6±3.28)
  - health (N=24; 27.1±5.23)
- Diagnosis determined using SCID
- Study site: State Pavlov Medical University, St. Petersburg, Russia

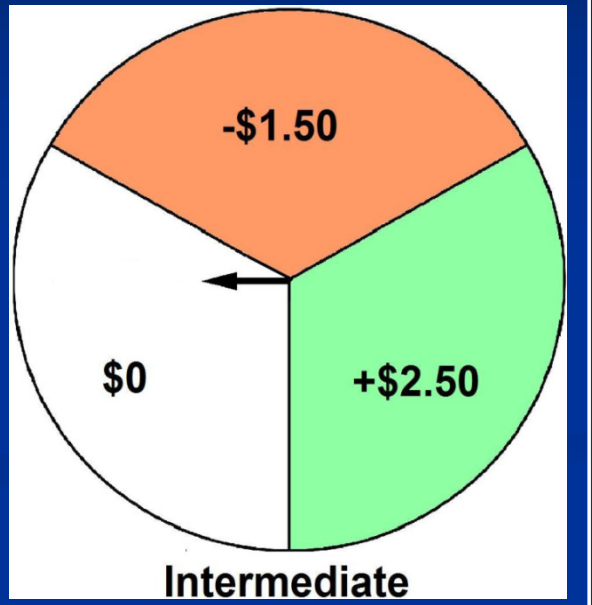
REWARD FUNCTION IN DRUG DEPENDENCE



MONETARY TASK







Wheel of fortune-type paradigm. Three different spinners are displayed: a “good” spinner that generates a large gain ($10), a small gain ($2.5) or no gain ($0); a "bad" spinner that generates a large loss ($6), a small loss ($2.5) or no loss ($0), and an "intermediate" spinner that generates a small gain ($2.5), a small loss ($1.5), or neither ($0). When the black arrow came to a stop in one of the spinner’s sectors, the subject experiences the indicated monetary gain or loss.

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Probing reward function in posttraumatic stress disorder: Expectancy and satisfaction with monetary gains and losses

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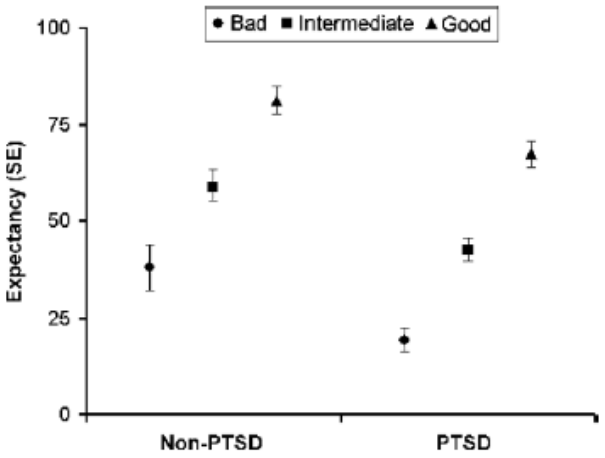


Fig. 2. Means and standard errors for self-report ratings of expected spinner outcomes, on a 100 mm horizontal visual analog scale with the anchors "very negative" and "very positive" at the far left (0) and right (100), respectively. Ratings were made during the expectancy phase of each trial, immediately after presentation of the spinner type for that trial (Fig. 1). See Section 2 for details.

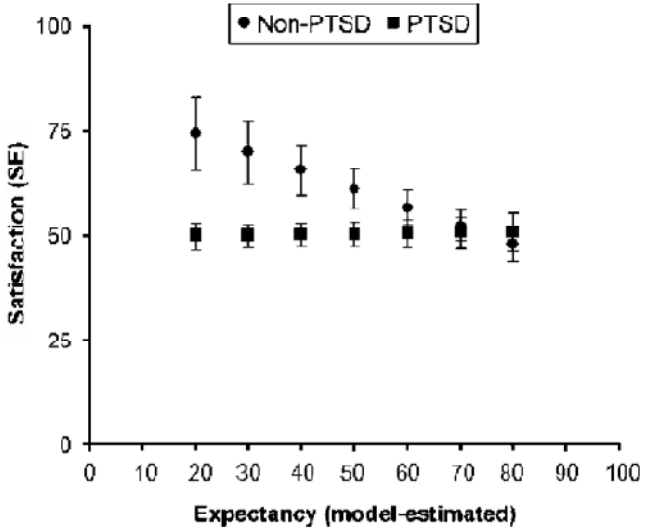


Fig. 3. Means and standard errors for self-report ratings of satisfaction with spinner results as a function of group and expectancy. Satisfaction with each spinner outcome was rated on a 100 mm VAS, with anchors of "not happy at all" and "very happy" at the far left (0) and right (100), respectively. See Section 2 for details.

ARCHIVAL REPORT

Functional Neuroimaging of Reward Circuitry Responsivity to Monetary Gains and Losses in Posttraumatic Stress Disorder

Igor Elman, Steven Lowen, Blaise B. Frederick, Won Chi, Lino Becerra, and Roger K. Pitman

Background: Clinical impressions and preclinical work suggest that posttraumatic stress disorder (PTSD) might be associated with dysfunctional reward processing. To pursue this issue, we administered a validated passive-viewing monetary reward task during functional magnetic resonance imaging (fMRI) to subjects with chronic PTSD and to mentally healthy individuals.

Methods: The protocol evaluated fMRI signal changes that anticipated or accompanied monetary gains and losses under varying conditions of controlled expectation. The "expectancy phase" entailed presentation of a promising, unpromising, or intermediate Wheel of Fortune–type spinner, whereas the "outcome phase" was defined by the arrow landing on one of three sectors of that spinner, thereby determining the subjects' gain or loss for that trial.

Results: Neuroimaging data from 20 PTSD and 26 healthy subjects withstood quality control procedures and were included. In voxelwise and anatomically defined region-of-interest analyses, when gains were contrasted to losses, between-group comparison revealed smaller bilateral striatal activations in the PTSD subjects. In the PTSD group, less striatal activation to gains versus losses was associated with more self-reported motivational and social deficits.

Conclusions: The present data support the hypothesis that PTSD is associated with abnormal processing of monetary outcomes and that this alteration might be related to some aspects of emotional numbing.

Key Words: Corpus striatum, functional magnetic resonance imaging, motivation, posttraumatic, reward, stress disorders

Anxiety symptoms are considered a key component in posttraumatic stress disorder (PTSD) (1), and most functional neuroimaging investigations in these patients have focused on the brain's fear system (2–4). However, recent research (5,6) also supports the inclusion of PTSD within a reward deficiency spectrum (7,8) comprising personality traits and mental disorders characterized by hypofunctionality of reward circuitry, and manifest as diminution of motivation and capacity to experience pleasure.

Several lines of evidence suggest deficits in the brain reward/reinforcement circuits in PTSD. From a clinical perspective, in addition to high prevalence of substance abuse (9), diagnostic features of PTSD itself suggest reward system dysfunction. The most notable of these are the "emotional numbing" symptoms, including anhedonia (i.e., loss of interest and pleasure) (1), which has been linked with reward function deficits in clinical (10) and mentally healthy (11) samples. The association between PTSD and reward deficits is also supported by animal findings of striatal dopaminergic hypoactivity (12,13) and decreased reward-seeking (14,15) resulting from chronic stress exposure in procedures that hypothetically (16) model the PTSD re-experiencing phenomenon (17).

To validate these clinical impressions and preclinical findings in a laboratory setting, we previously applied behavioral probes of reward function to PTSD subjects (5,6). In one study, we found that male heterosexual combat veterans with current PTSD exerted less effort to extend the viewing time of attractive female faces (5). In a second study, we investigated anticipatory and consummatory aspects of reward processing, assessed by subjective responses during a Wheel of Fortune–type game that provided passive monetary rewards. The PTSD combat veterans reported lower expectancy of and satisfaction with these rewards (6). Neuroimaging investigations have found that PTSD patients show less arousal (18) as well as smaller activations in temporal and parahippocampal brain regions (19) when exposed to pleasant images, and less activation in ventral striatum to positive feedback in a decision-making task (20).

Building upon our pilot behavioral findings (5,6), in the present experiment we used the same validated Wheel of Fortune–type monetary stimuli (6) in conjunction with blood-oxygen-level dependent (BOLD) functional magnetic resonance imaging (fMRI) to investigate the neural basis of decreased reward responsivity in PTSD. Notably, a previous study in healthy subjects reported significant fMRI signal changes obtained from dopamine terminal fields (striatum, amygdala, and prefrontal cortex) induced by processing of expectancy and experience of monetary gains and losses on this task (21). We hypothesized that PTSD would be associated with decreased fMRI signal in reward-related brain areas during both expectancy and outcome phases of the employed procedure.

Methods and Materials

Procedure

The experimental procedure is detailed elsewhere (21). Subjects were told that an arrow would spin around a disk (spinner) and come to rest in one of three differentially colored sectors representing monetary gains or losses (Figure 1). There were three different spinners: a "good" spinner that generated a large gain ($10.00), a small gain ($2.50), or no gain ($0.00); a "bad" spinner that generated a large loss ($6.00), a small loss ($1.50), or

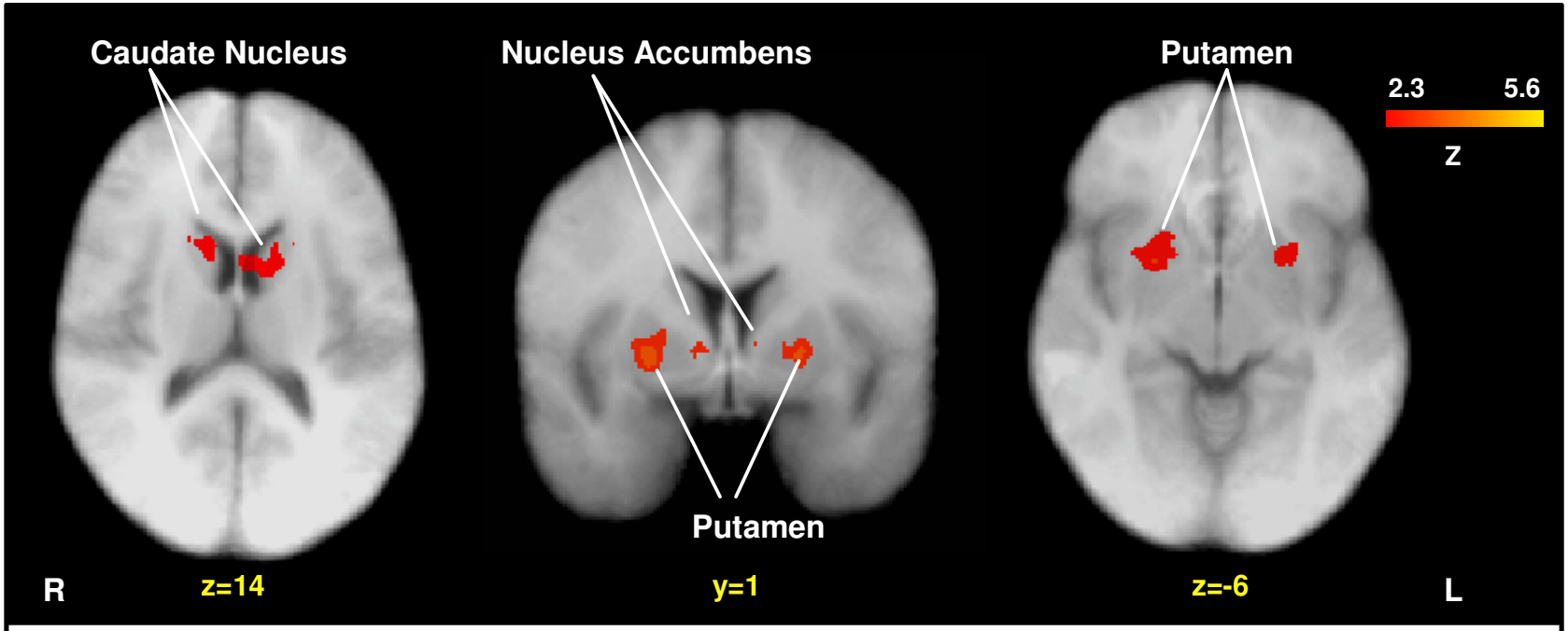
From the Clinical Psychopathology Laboratory (IE, WC) and Brain Imaging Center (IE, SL, BBF, LB), McLean Hospital and Harvard Medical School; and the Department of Psychiatry (RKP), Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts.

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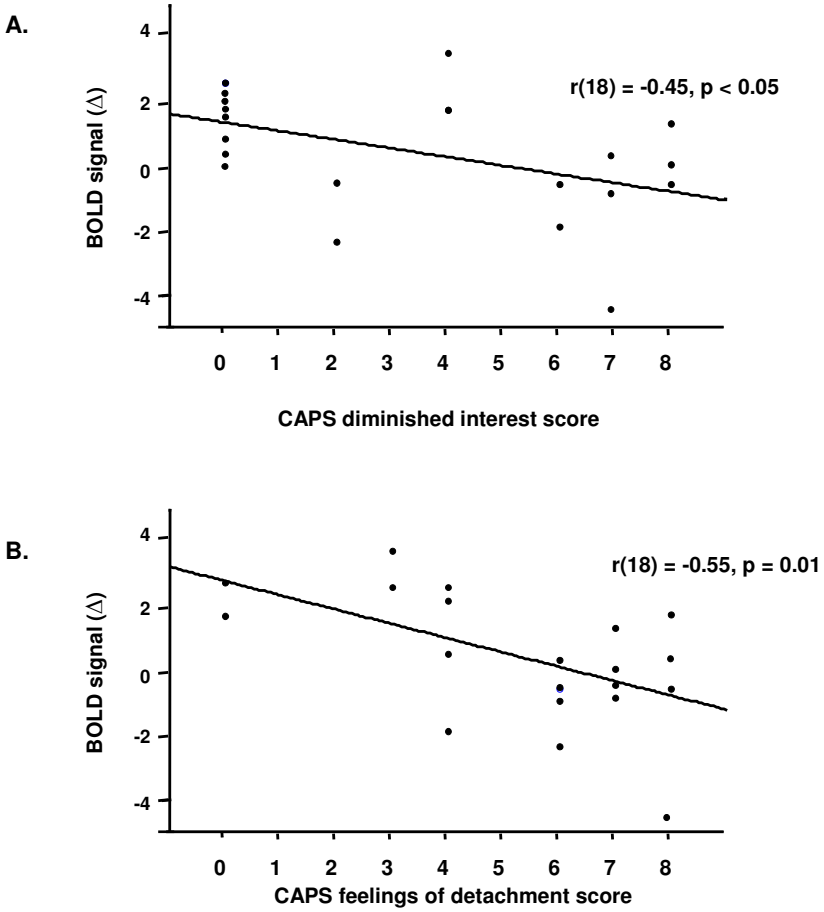
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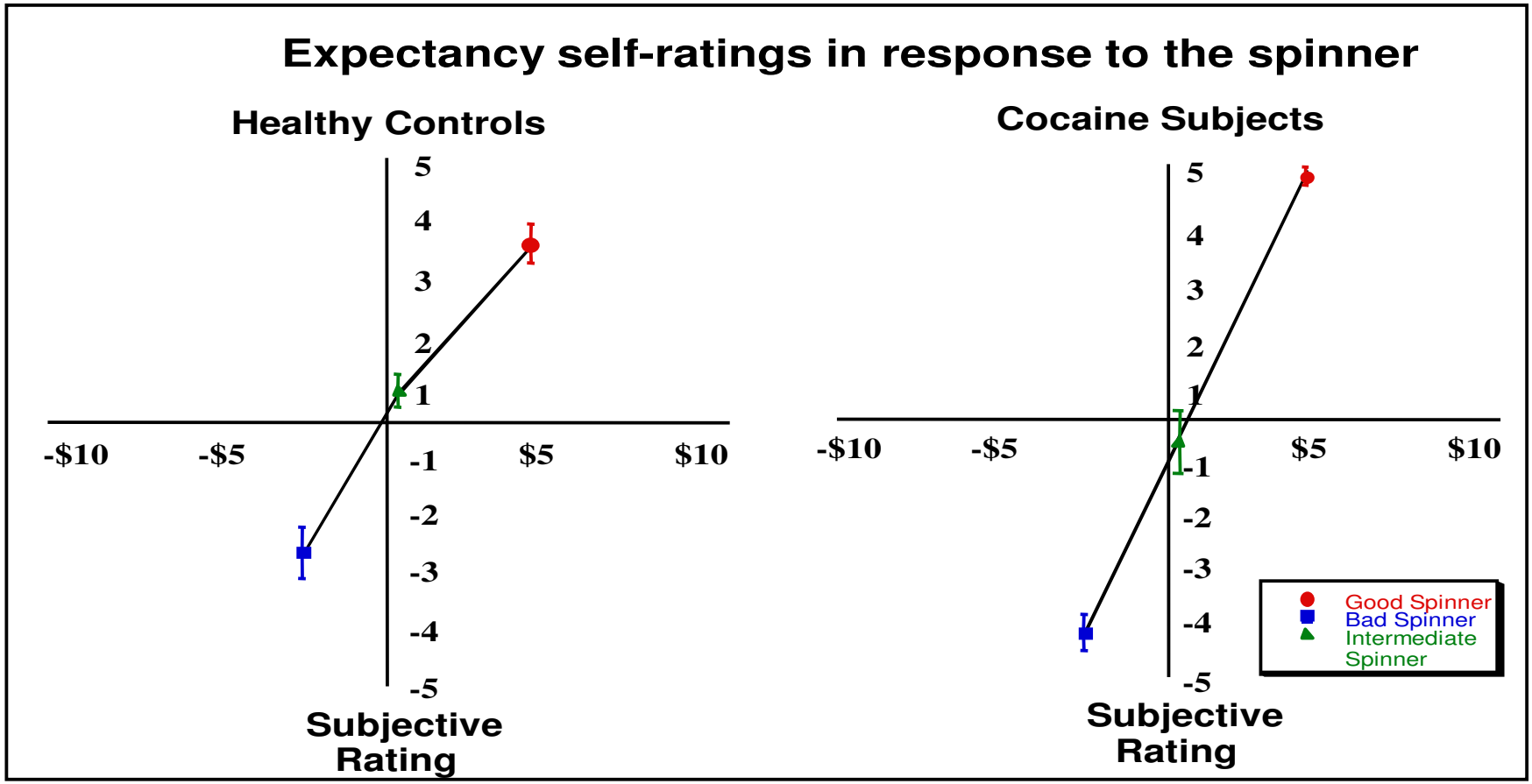


Clusters of activation in bilateral ventral and dorsal striatum obtained from voxelwise contrasts of monetary gains minus losses collapsed across spinner type in Control (N=26) > PTSD (N=20) subjects against a background representing the mean high-resolution anatomic image of the subjects included in the analysis. (Apparent activation in a ventricle represents artifact.) The x, y and z values are in accordance with the Harvard-Oxford subcortical structural atlas. A. Coronal view, B. Sagittal view and C. Axial views. (p<0.05 corrected)

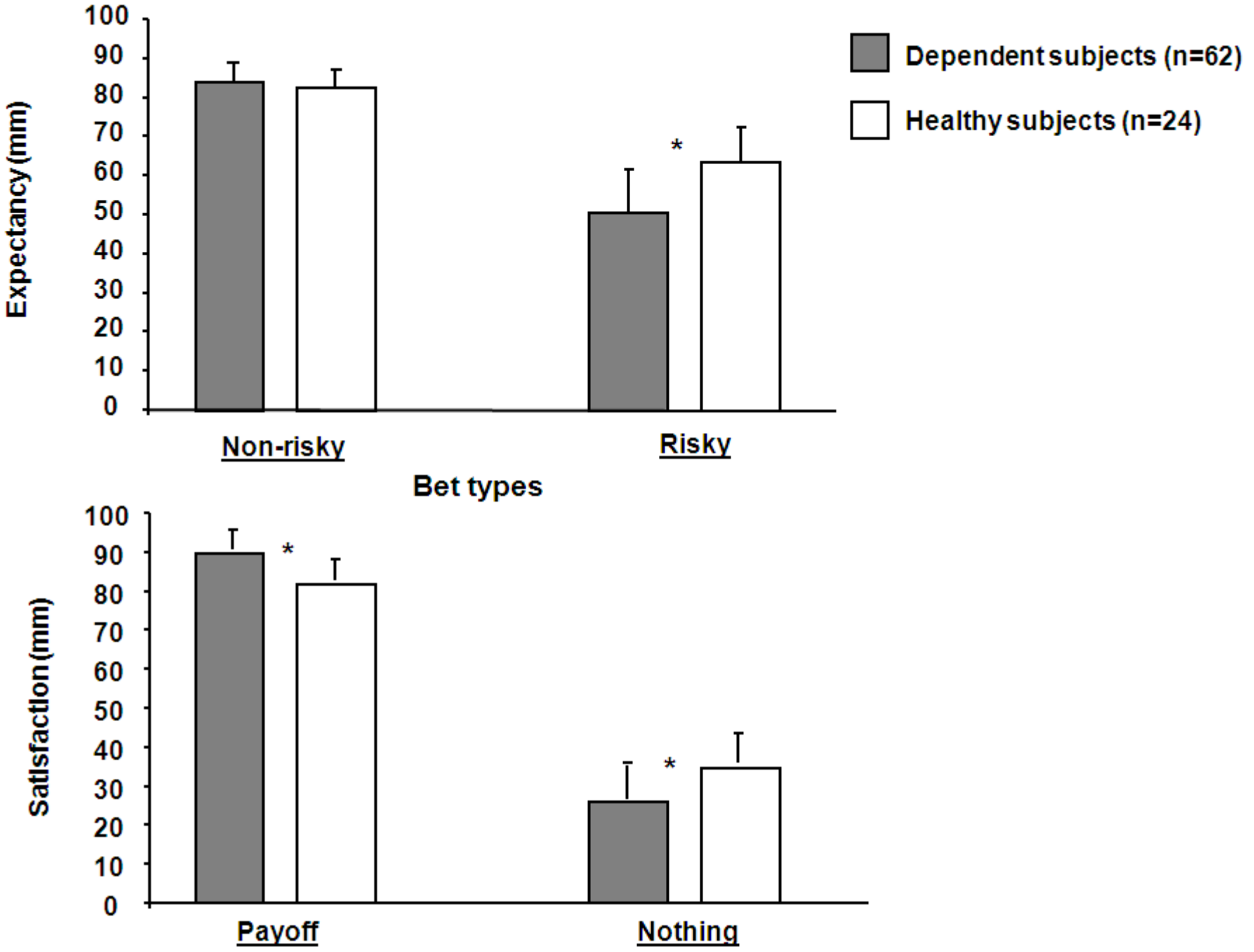
Scatterplots relating individual BOLD signal changes within PTSD subjects to their CAPS scores



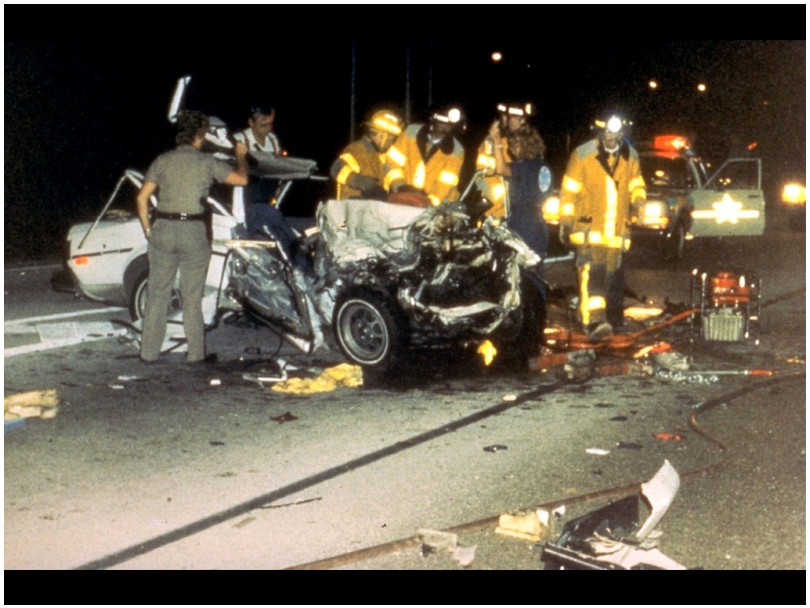
Subjective Responses on the Monetary Task in Cocaine Dependence (n=13, both groups)



more extreme range of responses to expectancy information i.e., overactive expectancy assessment

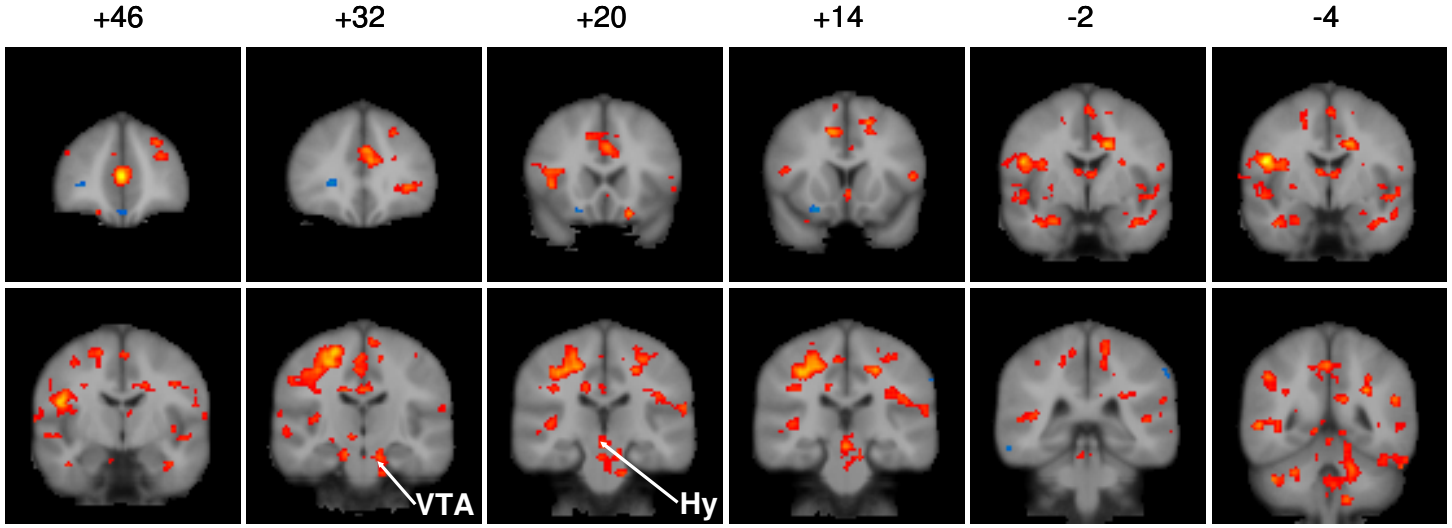

Dependent subjects (n=62)
Healthy subjects (n=24)
Expectancy (mm)
100
90
80
70
60
50
40
30
20
10
0
*
Non-risky
Risky
Bet types
Satisfaction (mm)
100
90
80
70
60
50
40
30
20
10
0
*
*
Payoff
Nothing

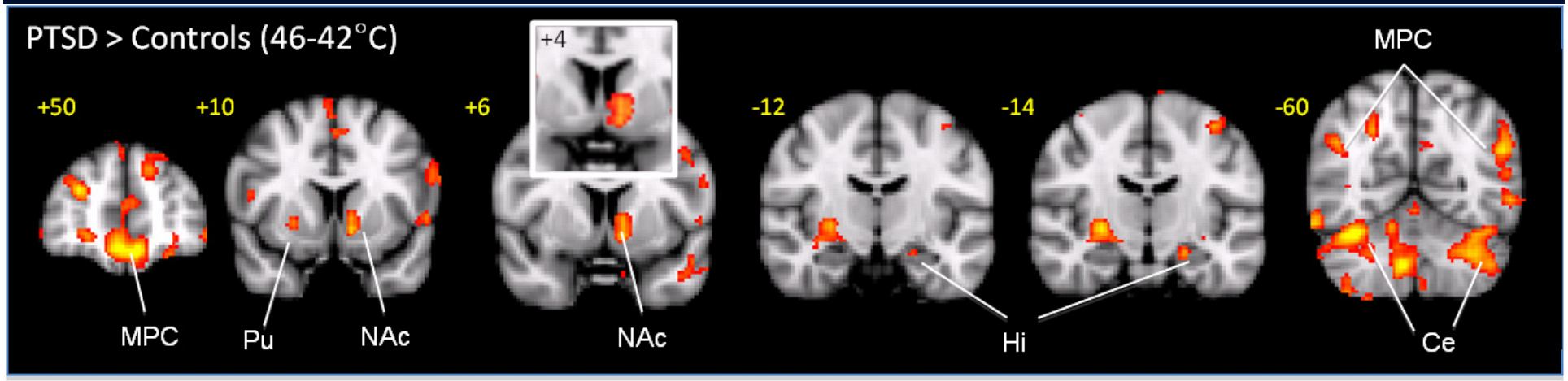
IAPS

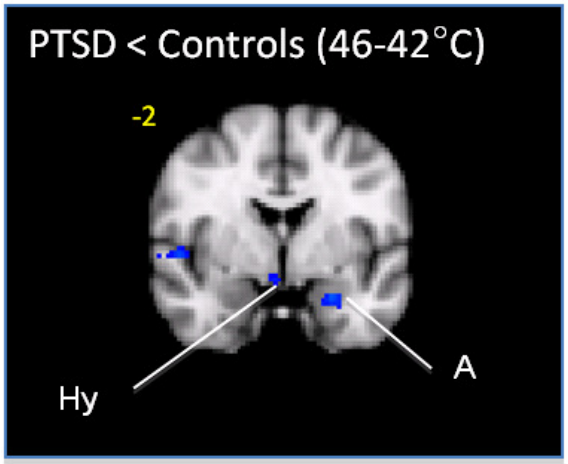




AVERSIVE IMAGES (PTSD aversive – PTSD neutral) – (CONTROL aversive – CONTROL neutral)

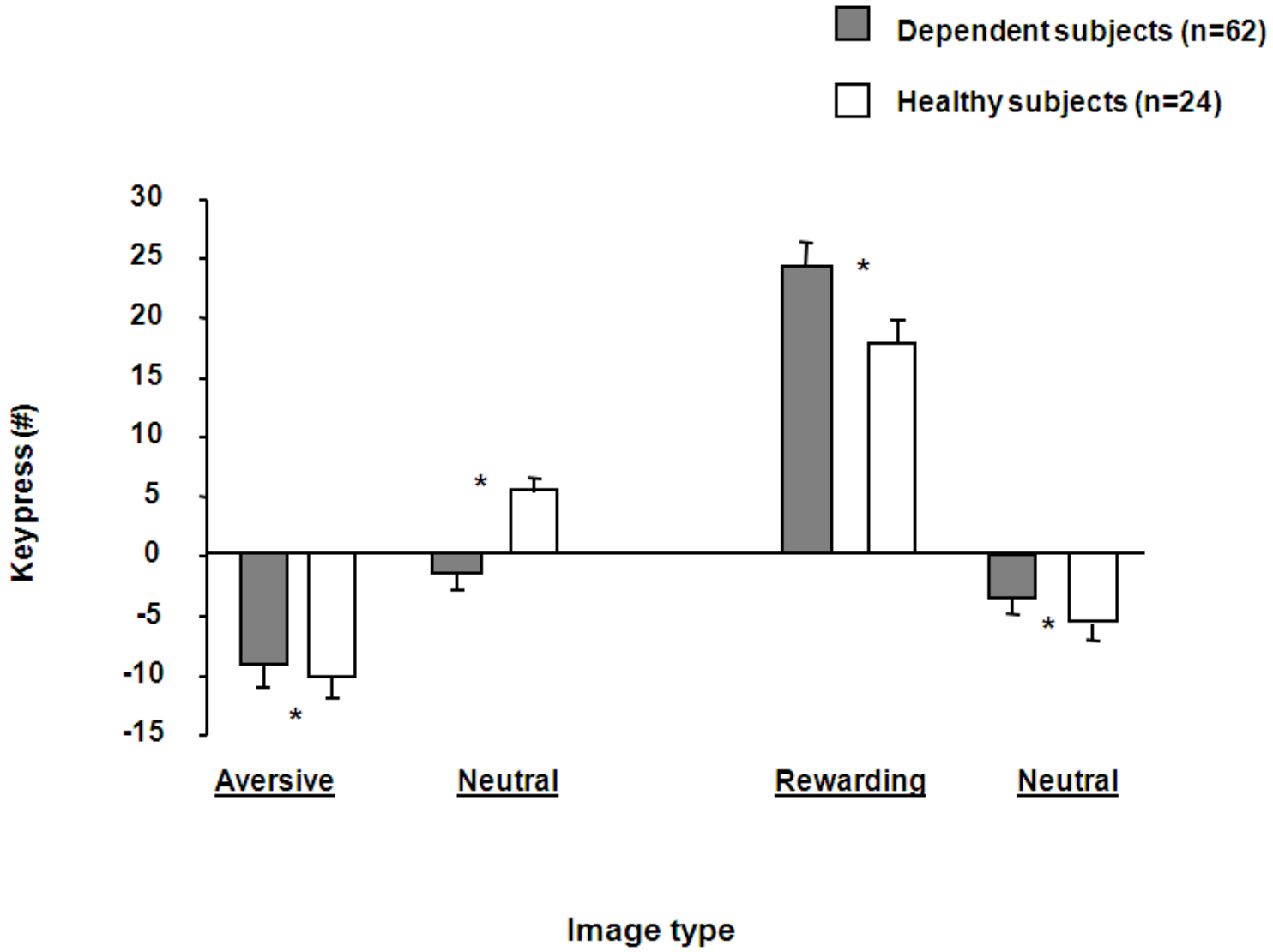






Sensitized to pain
Emotional Circuits
Dysregulation of NAc

AVERSIVE IAPS STIMULI



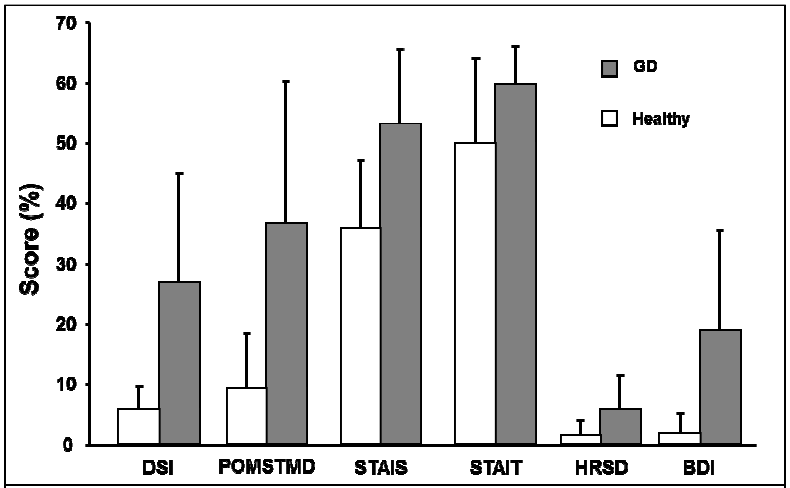
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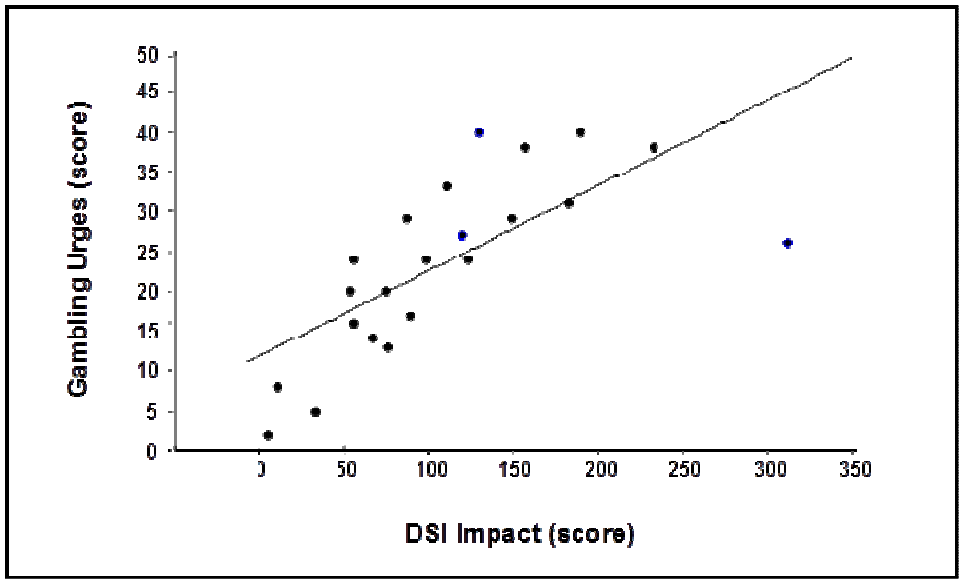
Psychosocial Stress and Its Relationship to Gambling Urges in Individuals with Pathological Gambling

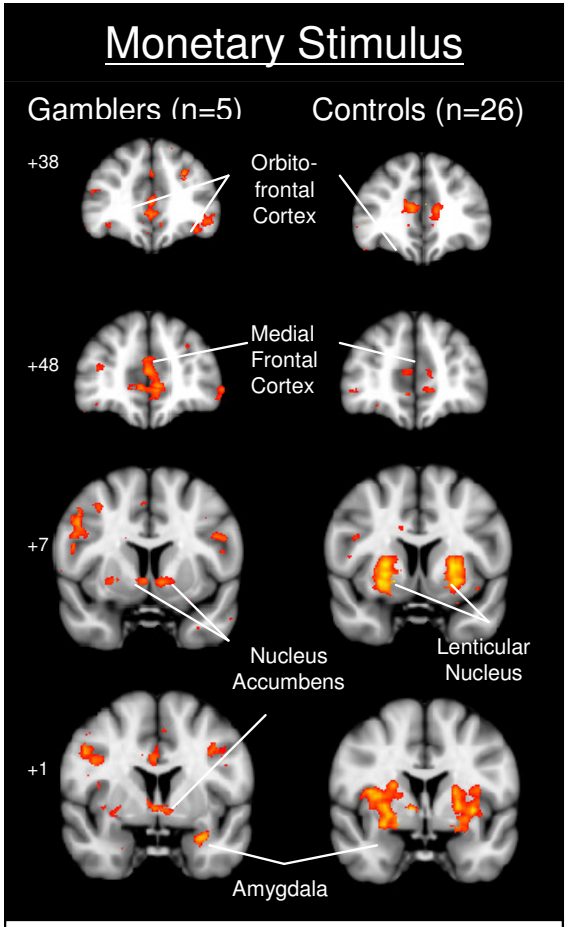
Igor Elman, MD, Evelyne Tschibelu, BS, David Borsook, MD, PhD

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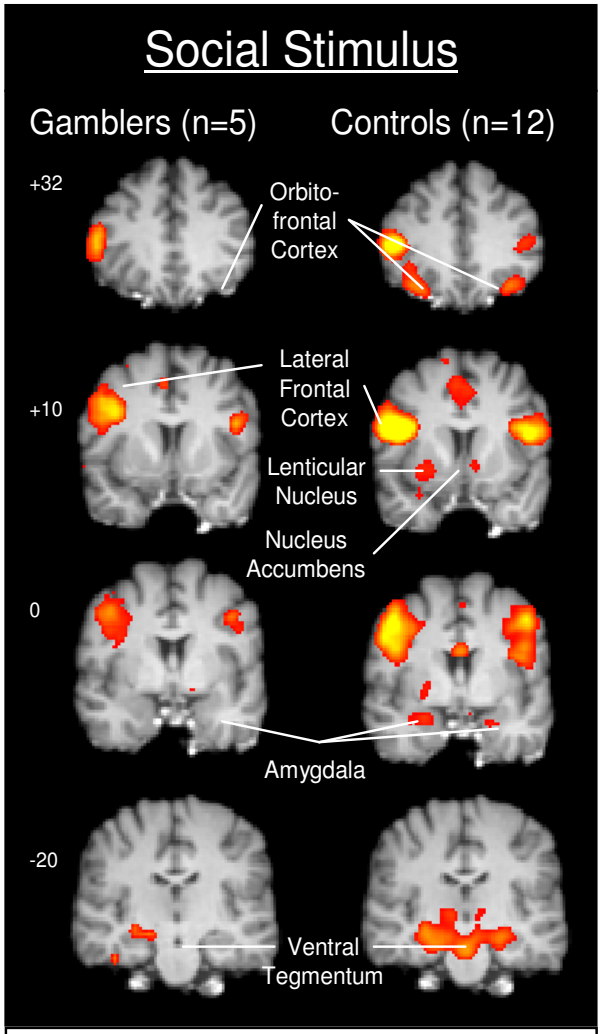


Group means±SDs for stress and negative affective states scales (adjusted for the maximal scores on the respective instruments). POMSTMD: the total mood disturbance score; STAIS: the state scale; STAIT: the trait scale

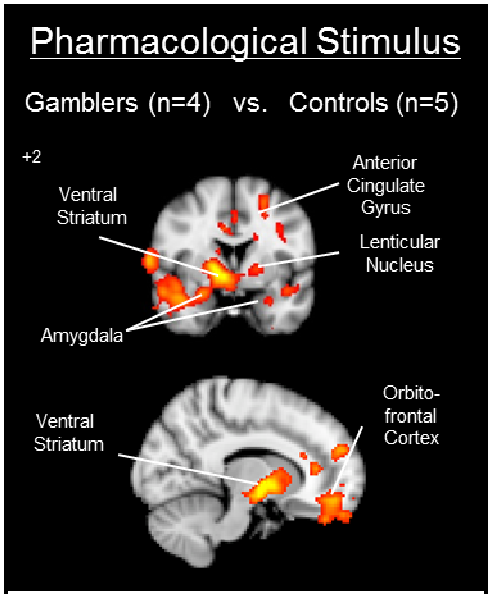




Activation maps (significance p <0.05 corrected) in gamblers (n=5) and controls (n=26) following a monetary stimulus (best possible outcome was contrasted with the worst possible outcome). Note that the data indicate potential differences in activation patterns. For example, there are differences in activation observed in the regions of interest (e.g., orbitofrontal cortex, nucleus accumbens and amygdala) in Gamblers.



Response to IAPS for rewarding picture stimuli. As is the case for the monetary stimuli, differences are observed in the regions activated in gamblers and in controls (p<0.05 corrected), The data seem to indicate a blunted response in Gamblers in regions such as the ventral tegmentum.



Difference map following yohimbine infusion in 4 subjects with gambling disorder and 5 controls. The data demonstrate increased activation in the regions of interest including ventral striatum, amygdala, and orbitofrontal cortex. p < 0.05, corrected.

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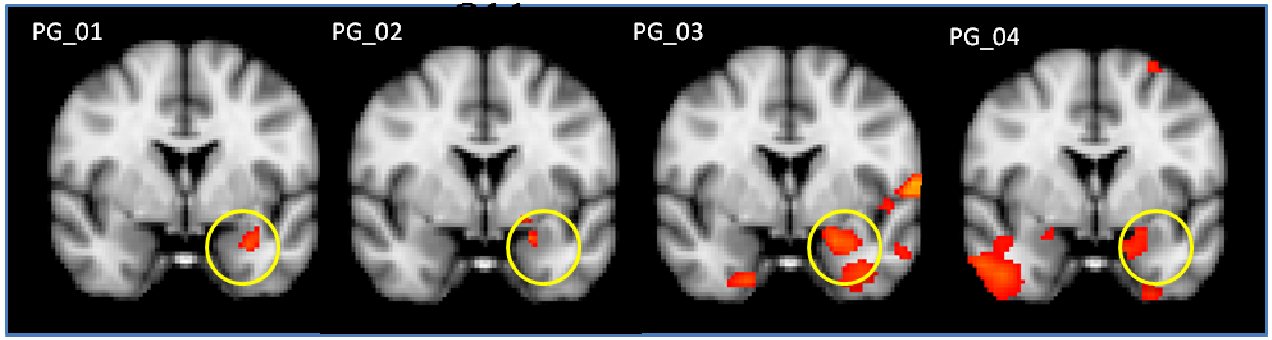
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Yohimbine-Induced Amygdala Activation in Pathological Gamblers: A Pilot Study

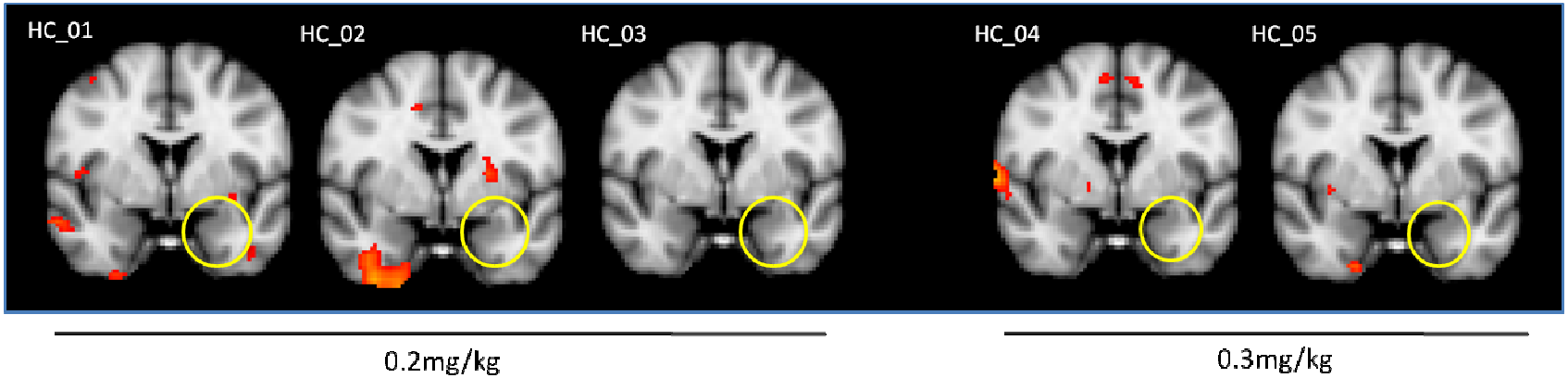
Igor Elman[1]*, Lino Becerra[2], Evelyne Tschibelu[3], Rinah Yamamoto[3], Edward George[2], David Borsook[2]

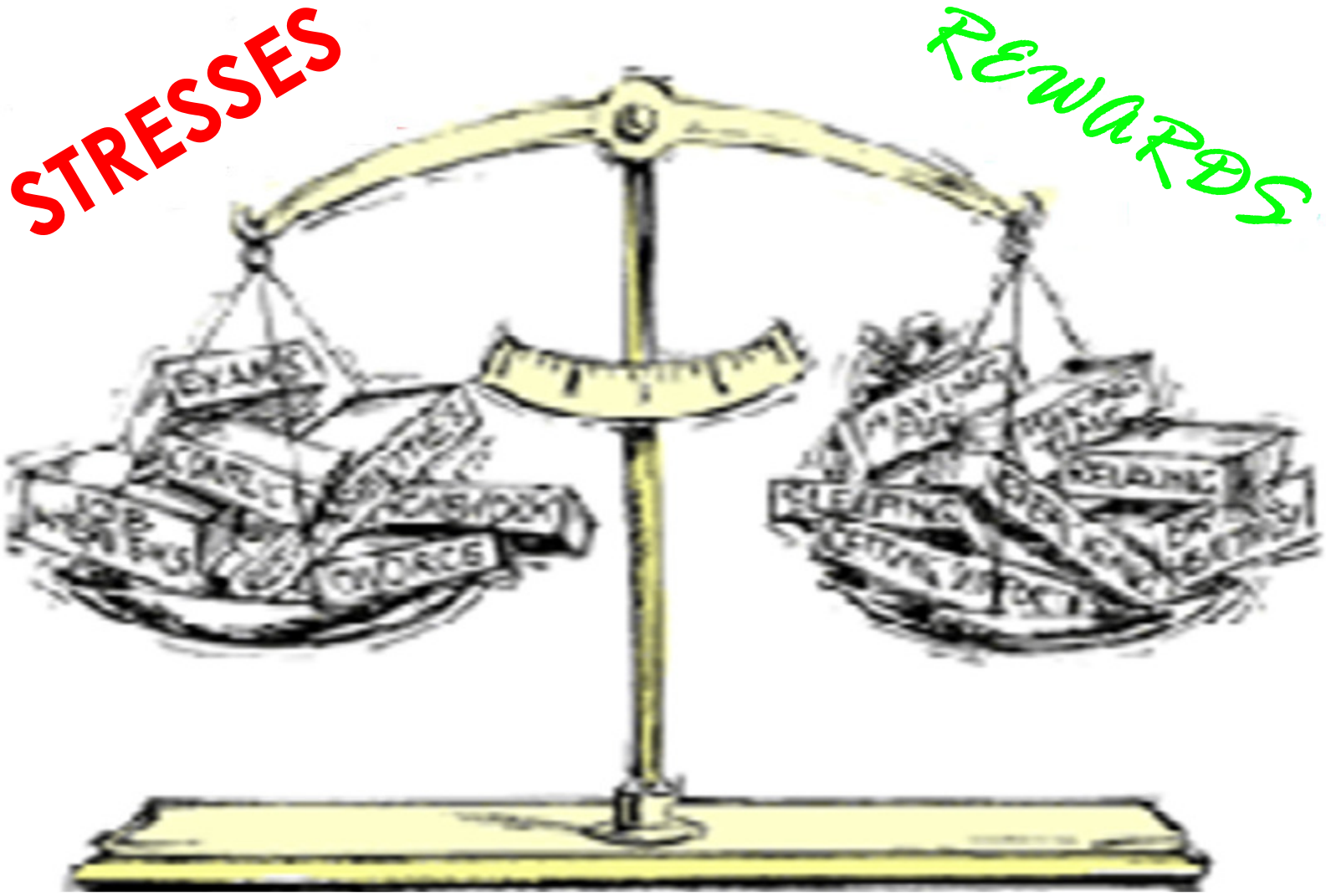
1 Bedford Veterans Administration Medical Center and Department of Psychiatry, Cambridge Health Alliance, Harvard Medical School, Somerville, Massachusetts, United States of America, **2** P.A.I.N Group, McLean Hospital and Harvard Medical School, Belmont, Massachusetts, United States of America, **3** Clinical Psychopathology Laboratory, McLean Hospital and Harvard Medical School, Belmont, Massachusetts, United States of America

Pathological Gamblers



Healthy Controls




STRESSES
REWARDS


Imbalance?

CONCLUSIONS

- Reward deficiency is amenable for clinical research using behavioral & neuroimaging procedures
- Reward deficiency is more readily demonstrable in PTSD & in GD than in chemical addictions
- Reward structures in the reward deficiency syndrome may actually be physiologically normal, but are not being adequately ‘recruited’ because of factors involved in their processing of stress

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- MIT: Dan Ariely & Nina Mazar
- State Pavlov Medical University, St. Petersburg: Edwin Zvartau & Evgeny Krupitsky
- NIDA Support: DA17959 (IE)

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Addiction Therapy – 2015 Website:

addictiontherapy.conferenceseries.com