Functional magnetic resonance imaging of internet addiction in young adults

Gianna Sepede, Margherita Tavino, Rita Santacroce, Federica Fiori, Rosa Maria Salerno, Massimo Di Giannantonio

AIM: To report the results of functional magnetic resonance imaging (fMRI) studies pertaining internet addiction disorder (IAD) in young adults.

METHODS: We conducted a systematic review on PubMed, focusing our attention on fMRI studies involving adult IAD patients, free from any comorbid psychiatric condition. The following search words were used, both alone and in combination: fMRI, internet addiction, internet dependence, functional neuroimaging. The search was conducted on April 20th, 2015 and yielded 58 records. Inclusion criteria were the following: Articles written in English, patients' age ≥ 18 years, patients affected by IAD, studies providing fMRI results during resting state or cognitive/emotional paradigms. Structural MRI studies, functional imaging techniques other than fMRI, studies involving adolescents, patients with comorbid psychiatric, neurological or medical conditions were excluded. By reading titles and abstracts, we excluded 30 records. By reading the full texts of the 28 remaining articles, we identified 18 papers meeting our inclusion criteria and therefore included in the qualitative synthesis.

RESULTS: We found 18 studies fulfilling our inclusion criteria, 17 of them conducted in Asia, and including a total number of 666 tested subjects. The included studies reported data acquired during resting state or different paradigms, such as cue-reactivity, guessing or cognitive control tasks. The enrolled patients were usually males.
Internet addiction disorder (IAD), also called pathologic/internet gaming disorder (IGD) (also called videogame addiction), is included in the section 3 as a topic deserving future studies[2]. A recent meta-analysis on IAD[3] involving more than 89000 participants from 31 nations reported a global prevalence estimate of 6%, with the higher prevalence in the Middle East (10.9%) and the lowest prevalence in Northern and Western Europe (2.6%). A higher prevalence of IAD was significantly associated with lower subjective and environmental conditions. A recent study conducted on Indian college students[4] reported 8% of moderate IAD and identified the following variables as risk factors: Male gender, continuous availability online, using the internet more for making new friendships/relationships and less for coursework/assignment. Due to their high computer skill and easy Internet access, young adults are at augmented risk for IAD[5].

Some of the clinical characteristics of IAD are similar to those observed in behavioral or substance misuse disorders (loss of control, craving, withdrawal symptoms), Obsessive Compulsive Disorder, or Bipolar Disorder so the nature of IAD (primary psychiatric disorder or “online variant” of other psychiatric conditions) is still debated[6-9].

Functional imaging techniques increase the possibility to investigate the neural basis of IAD, enhancing the sensitivity and the statistical power of clinical data. Functional magnetic resonance imaging (fMRI), in particular, is a worldwide used non-invasive technique to study the neural underpinnings of psychiatric disorders[10-12]. By means of fMRI, brain signal changes may be analyzed in terms of functional fluctuations with respect to a given “baseline” (activations/deactivations analysis) or in terms of functional connectivity among different brain regions (network analysis). Metabolic activity changes in the brain can be monitored during the execution of paradigms (task related fMRI) or during the spontaneous cerebral activity (resting state fMRI)[13-16].

Aim of the present study was to systematically review the resting state and task related fMRI studies conducted on adult subjects with IAD, looking for reliable biomarkers of this challenging mental condition.

MATERIALS AND METHODS

We searched PubMed to identify fMRI studies investigating IAD in adult subjects. The following search words were used, both alone and in combination: fMRI, Internet addiction, Internet dependence, functional neuroimaging. The search was conducted on April 20th, 2015 and yielded 58 records.

Inclusion criteria were the following: Articles written in English, patients’ age ≥ 18 years, patients affected by IAD, studies providing fMRI results during resting state or cognitive/emotional paradigms. Structural MRI studies, functional imaging techniques other than fMRI, studies involving adolescents, patients with comorbid psychiatric, neurological or medical conditions were excluded.

INTRODUCTION

Internet addiction disorder (IAD), also called pathologic/problematic internet use (PIU), may be defined as an impulse control disorder characterized by an uncontrolled Internet use, associated with a significant functional impairment or clinical distress[5]. IAD is not classified as a mental disorder in the Diagnostic and Statistical Manual of Mental Disorders-fifth edition, but a subtype of IAD, the internet gaming disorder (IGD) (also called videogame addiction), is included in the section 3 as a topic deserving future studies[2].
Sepede G et al. Neuroimaging of internet addiction

Figure 1  Flow diagram of the systematic review.

excluded.

By reading titles and abstracts, we excluded 30 records. By reading the full texts of the 28 remaining articles, we identified 18 papers meeting our inclusion criteria and therefore included in the qualitative synthesis (Figure 1).

Biostatistics
Statistics were performed by Dr. Gianna Sepede, who has a certificated experience in Biomedical Statistics, Systematic Reviews and Meta-analysis. In the present paper, PRISMA 2009 checklist (http://www.prisma-statement.org/) was used to describe eligibility criteria, conduct the search, select the studies and report the qualitative synthesis results. Statistical methods were therefore adequately described, correct and conducted on homogeneous data. Number of subjects and dropouts were given. When appropriate, confidence limits and significant P values were calculated and reported.

RESULTS
We found 18 papers fulfilling our inclusion criteria, all published from 2009 to 2015[17-35]. The studies were all conducted in the Asian Continent (China, South Korea, Taiwan), with the only exception of the paper published by Lorenz et al[23], which was conducted in Germany.

In total, 666 subjects were tested by the 18 studies included in the qualitative synthesis: 347 patients with IAD (IADp), 304 normal comparisons (NC) and 15 subjects with Alcohol Use Disorder (AUDp). The large majority of IADp were male (n = 331, 95.4%) and very young (mean age ranged from 21 to 25 years). The number of patients involved in each study ranged from 8 to 74. For what regards the subtypes of IAD, 15 out of 18 studies focused on IGD[19-24,26-34], so more than 85% of all the IADp (n = 297) were IGD patients (IGDp). Different diagnostic criteria were used to assess IAD, such as Beard’s Diagnostic criteria for Internet addiction[35], Ko’s diagnostic criteria of Internet addiction for college students[36], Chinese Internet addiction test (C-IAT)[37] and Grüsser and Thalemann’s computer game addiction criteria[38].

The most used questionnaire to assess the severity of IAD was the Young’s IAT[11], with different cut-off (usually > 80, in a few studies > 50). To diagnose IGD, online gaming was also required to be the principal Internet activity (more than 80% of the time spent online or more than 30 h/wk).

In order to exclude subjects with comorbid psychiatric conditions or substance use disorders, structured interviews and psychometric scales to address depression, anxiety, impulsivity, substance addiction were usually provided.

MRI data were acquired with a 3 T scanner in 17 studies, and with a 1.5 T scanner in one study[19]. In 4 articles, only resting state fMRI was recorded, whereas 13 articles reported task related fMRI data, and one paper acquired both resting state and task related functional activations[31]. Seventeen studies were transversal observational reports, whereas the paper by Han et al[35] was a 6-wk longitudinal study.

The participants in the 18 selected studies were all free of any psychopharmacological treatment at the moment of the scanning (and at study enter for the above mentioned longitudinal study).

Resting state fMRI studies on IAD
A total number of five studies were selected[18,21,31,32,34]. The characteristic of the groups and the results of the studies are reported in Table 1. Right-handedness was an inclusion criterion in 4 studies[18,21,31,34], as well as male gender[21,31,32,34]. A total number of 298 subjects (Males n = 280, 94%), all medication free, were involved: 159 IADp (140 IGDp), 124 NC and 15 AUDp. Patients were usually very young (mean age ranging from 21 to 24 years).

In all the five selected studies, fMRI images were acquired using a 3 T scanner and scan duration ranged from 7 to 9 min. Resting state functional connectivity (RsFc) and/or Regional Homogeneity (ReHo) were calculated to assess between group differences. As a result, all the selected studies identified significant differences between patients and controls.

Liu et al[18], in their research on 19 IAD patients, reported an increased synchronization among frontal areas, cingulate gyrus, temporal and occipital regions, cerebellum and brain stem, with respect to matched normal comparisons. So the authors suggested an altered functional connectivity in regions belonging

Table 1 Inclusion criteria of resting state fMRI studies on IAD

| Study | Inclusion criteria | Exclusion criteria |
|-------|-------------------|-------------------|
| [18]  | Right-handedness | Subjects with comorbid psychiatric conditions or substance use disorders. |
| [21]  | Right-handedness | Subjects with comorbid psychiatric conditions or substance use disorders. |
| [31]  | Right-handedness | Subjects with comorbid psychiatric conditions or substance use disorders. |
| [32]  | Right-handedness | Subjects with comorbid psychiatric conditions or substance use disorders. |
| [34]  | Right-handedness | Subjects with comorbid psychiatric conditions or substance use disorders. |

Records identified through PUBMED searching (n = 58)

Records excluded (n = 30)

Full-text articles assessed for eligibility (n = 28)

Full-text articles excluded, with reasons (n = 9)
Comorbid psychiatric conditions (n = 5)
Not involving clinical internet addiction disorder patients (n = 3)
Unavailable/incomplete data (n = 2)

Studies included in qualitative synthesis (n = 18)
### Table 1  Resting state functional magnetic resonance imaging studies in internet addiction disorder

| Ref. | Design and aims | Participants | Diagnostic criteria and evaluation scales | fMRI methods | fMRI results |
|------|-----------------|--------------|------------------------------------------|--------------|-------------|
| Liu et al[24] | Resting state fMRI study  
Aim: To analyze encephalic functional characteristic of IAD under resting state | n = 38, age range 18-25 yr  
Males 100%  
Right-handed 100%  
Medication free 100%  
Normal neurological examination 100%  
No comorbid psychiatric disorders  
Groups: ICA n = 19  
Mean age: 21.0 ± 1.3 yr  
Males n = 11 (57.9%)  
NC n = 19 (50%)  
Mean age: 20.0 ± 1.8 yr  
Males n = 11 (57.9%) | IAD: Beard's DQA ‘5 + 1 criteria’ plus any one of:  
≥ 6 h/d for 3 mo  
Decline in academic performance  
Unable to maintain normal school learning  
Signal analyzed by means of KCC  
ReHo measured by ROI based analysis | Scanner: 3 T  
FMRI Scan duration: 9 min  
Software used: SPM2, ReHo  
Both whole brain and ROI based analysis | Between group significant effects:  
ReHo  
IAD > NC in: Cerebellum, brainstem, R CG, bilateral PH, R PL, L SFG, L precuneus, R PoCG, R MOG, R ITG, L STG, MTG |
| Dong et al[25] | Resting state fMRI study  
Aim: To investigate the effects of long-time online game playing on visual and auditory brain regions | n = 29, age 24.2 ± 3.8 yr  
Males 100%  
Right-handed 100%  
Medication free 100%  
No nicotine, cocaine or marijuana use  
Groups: IGD n = 15;  
Age 24.2 ± 3.3 yr  
NC n = 14;  
Age 24.6 ± 3.8 yr | IGD: YIAT ≥ 80  
> 80% of the online time was spent playing videogames  
BDI < 5;  
MINE: No Axis I psychiatric disorders  
ReHo measured by means of KCC  | Scanner: 3 T  
FMRI Scan duration: 9 min  
Software used: DPARSF, SPM8, ReHo  
Both whole brain and ROI based analysis | Between group significant effects:  
ReHo  
IGD > NC in: Bilateral brainstem, bilateral IPL, L posterior cerebellum, R MfCG;  
IGA < NC in: L STG, L ITG, L OL, L PL |
| Dong et al[26] | Resting-state and task related fMRI  
Aim: To examine the FC of ECN during both resting state and Stroop task performing | n = 71  
Age 22.35  
Males 100%  
Right-handed 100%  
Medication free 100%  
No DSM 5 psychiatric disorders  
Groups: IGD n = 35  
Age 22.2 ± 3.8 yr  
NC n = 36  
Age 22.8 ± 2.4 yr  
Males 100%  
Right-handed 100%  
Medication free 100%  
No DSM 5 psychiatric disorders  
Groups: IGD n = 35  
Age 22.2 ± 3.8 yr  
NC n = 36  
Age 22.8 ± 2.4 yr  | IGD: Young’s IAT ≥ 50  
> 80% of the online time was spent playing videogames  
BDI < 5;  
MINE: No Axis I psychiatric disorders  
ReHo measured by means of KCC  | Scanner: 3 T  
Rs fMRI Scan duration: 7 min  
Software used: REST, DPARSF, SPM8, FSL  
Signal analyzed by ROI based analysis | Between group significant effects:  
ReHo  
IGD < NC in: Total ECN and L ECN |
| Kim et al[27] | Resting state fMRI study  
Aim: To compare the brain functioning of IGD, AUD, and NC during resting state | n = 45  
Age 21.6 ± 5.9 yr  
Males 100%  
Right-handed 100%  
Medication free 100%  
Groups: IGD n = 16  
Age 21.6 ± 5.9 yr  
AUD n = 14  
Age 28.6 ± 5.9 yr  
NC n = 15  
Age 25.4 ± 5.9 yr  | For all participants:  
WAIS III ≥ 80  
For IGD: YIAT ≥ 70  
> 4.5 h/d were spent playing online  
For AUD: SCID criteria  
AUDIT-K < 2 h/d were spent online  
Other scales administered to all subjects:  
BDI, IGD and AUD > NC (P < 0.01)  
BAI, AUD > NC (P < 0.01)  
BS-11: IGD and AUD > NC (P < 0.01) | Scanner: 3 T  
Rs fMRI Scan duration: 8 min  
Software used: DPARSF, SPM8, REST  
ReHo measured by means of KCC  | Between group significant effects:  
ReHo  
(1) IGD vs NC  
IGD > NC in L PPC  
IGD > NC in R STG  
(2) IGD vs AUD  
IGD > NC in R STG  
(3) AUD vs NC  
AUD > NC in R PCC, R insula, L MTG  
AUD < NC in R ACC |
| Zhang et al[28] | Resting state fMRI in young adults with Internet gaming disorder using rsFC  
Aim: To study resting-state functional connectivity of the insula in IGD | n = 115  
Males 100%;  
Medication free 100%  
Right-handed 100%;  
Groups: IGD n = 74  
Age 22.3 ± 2 yr;  
n = 57 alcohol drinkers  
Age 23.0 ± 2.1 yr  
n = 8 cigarette smokers  
NC n = 41;  
age 23.0 ± 2.1 yr  
n = 29 alcohol drinkers  | IGD: CIAS ≥ 67  
Internet gaming > 14 h/wk for 1 yr  
Playing as the principal online activity  
NC: CIAS < 60  
internet gaming < 2 h/wk  
Other scales: FTND  
BDI: IGD > NC  | Scanner: 3 T  
Rs fMRI Scan duration: 7 min  
Software used: DPARSF, REST, SPM8  
Signal analyzed by ROI based analysis | Between group significant effects:  
ReHo  
L anterior insula  
IGD > NC in R putamen, R angular gyrus, IFG  
R anterior insula;  
IGD > NC in ACC, middle CG, L angular gyrus, L precuneus, Bilateral SFG and STG  
L posterior insula  
IGD > NC in bilateral PoCG, L |

---

**Aim:** To examine the functional connectivity of the insula in IGD

**Participants:**
- **IGD:** 74
- **NC:** 41

**Diagnostic criteria and evaluation scales:**
- **IGD:**
  - CIAS ≥ 67
  - Internet gaming > 14 h/wk for 1 yr
  - Playing as the principal online activity

**fMRI methods:**
- **Scanner:** 3 T
- **Rs fMRI Scan duration:** 7 min
- **Software used:** DPARSF, REST, SPM8

**fMRI results:**
- **Signal analyzed by ROI based analysis**
to the reward system of the brain. All the four papers focused on IGD patients reported significant between group effects. Dong et al. observed that, when compared to controls, IGD patients showed an enhanced ReHo in sensorimotor coordination areas (brainstem, cerebellum, bilateral inferior parietal lobule, and left middle frontal gyrus), and a reduced ReHo in left-sided visual and auditory cortex. In a larger sample of IGD patients, Dong and colleagues observed a reduced functional connectivity in areas belonging to the Executive Control Network, especially in the left hemisphere: Ventromedial prefrontal cortex, dorsolateral prefrontal cortex and parietal cortex.

In a recent study, Kim et al. compared the resting state brain functioning of IGD patients not only with healthy subjects, but also with a group of AUD patients, looking for similarities and differences between these two “addictive conditions”. As a result, they found that both IGD and AUD shared an augmented ReHo in posterior cingulate cortex with respect to healthy controls, whereas a reduced ReHo in the right superior temporal gyrus was observed in the IGD patients only. The authors also reported a negative correlation between the left inferior temporal cortex and the level of impulsivity.

To assess the role of the insular cortex in IGD, Zhang et al. conducted a seed-based resting state connectivity study in 74 patients with IGD and compared them with 41 normal controls. IGD patients exhibited enhanced rsFC between the anterior insula and anterior cingulate cortex, precuneus, angular gyrus and basal ganglia (all areas involved in cognitive control, salience, attention and craving). When analyzing the posterior part of the insula, they found an augmented rsFC in areas playing a key role in sensory-motor integration, such as post central and precentral gyrus, supplementary motor area and superior temporal gyrus. Moreover, they observed a positive correlation between the insula-superior temporal gyrus connectivity and the level of IGD severity.

Summarizing the rsfMRI studies, the more relevant abnormalities observed in IGD were localized in the superior temporal gyrus. Other important alterations were detected in limbic areas, medial frontal regions (anterior cingulate cortex, supplementary motor area) and parietal regions. Results in not gaming IAD were limited due to the small number of patients involved (n = 19) and reported altered functioning in reward-related brain regions (frontal, parietal, temporal regions, cingulated gyrus, brain stem and cerebellum).

Task-related fMRI studies on IAD

We found 14 studies reporting task-related neural correlates of IAD. The characteristic of the groups and the results of the studies are reported in Table 2. Right-handedness was an inclusion criterion in all but two studies. Only male participants were included in 13 studies, whereas a mixed gender sample was enrolled by Liu et al. (2015). A total number of 368 subjects (males n = 352, 95.6%: Mean age ranging from 21 to 25 years) were involved: 188 IADs (IGDs n = 157) and 180 NC. Participants were all medication free at the moment of the scanning and at study enter for the longitudinal study by Han et al. (2015). FMRI images were acquired using a 3 T scanner and scan duration ranged from 5 to 30 min.

The paradigms administered to the participants were: cue-reactivity tasks (three studies), guessing tasks (three studies), cognitive control tasks of different kinds (eight studies). In more than half of the studies, no behavioral differences were found between cases and controls, but all of them reported significant group effects in functional activation of several brain regions, especially orbitofrontal gyrus, anterior cingulate cortex, insula, dorsolateral prefrontal cortex, precuneus, posterior cingulate cortex and superior temporal gyrus.

In cue-reactivity paradigms, addicted subjects are exposed to stimuli designed to elicit a craving for substance or behavior: In case of IAD, i.e., viewing images or videos related to videogames or Internet scenarios.

In probabilistic guessing tasks, participants are required to bet on different outcomes (i.e., on cards, dice, colors) and their brain response to win or loss
| Ref.                        | Design and aims                                                                 | Participants              | Diagnostic criteria and evaluation scales | Task and behavioral results                                                                 | fMRI methods                          | fMRI results                                                                                     |
|---------------------------|---------------------------------------------------------------------------------|---------------------------|------------------------------------------|------------------------------------------------------------------------------------------------|---------------------------------------|-------------------------------------------------------------------------------------------------|
| Ko et al[17]              | Task related fMRI study                                                         | n = 20; Males 100%        | DCIA-C                                   | Task used: Cue-reactivity paradigm. Task design: Videogame viewing Behavioral results: Gaming craving: IGD > NC | Scanner: 3 T                          | Between group significant effects: IGD > NC in: R OFC, R basal ganglia (caudatum and accumbens), bilateral ACC, bilateral MFG, R DLPFC |
|                           | Aim: To identify the neural substrates of IGD by means of a cue-reactivity paradigm | Medication free 100%     | MINI                                     | fMRI scan duration: 4.8 min Acquisition method: Block design Software used: SPM2                | Signal analyzed: BOLD                  |                                                                                  |
|                           |                                  | Right-handed 100%         | CIAS                                     |                                                                                                 |                                       |                                                                                  |
|                           |                                  | Normal neurological      | AUDIT                                    |                                                                                                 |                                       |                                                                                  |
|                           |                                  | examination 100%          |                                          |                                                                                                 |                                       |                                                                                  |
|                           |                                  | No comorbid psychiatric disorders or substance use                            |                                          |                                                                                                 |                                       |                                                                                  |
|                           |                                  | Groups: IGD n = 10        |                                          |                                                                                                 |                                       |                                                                                  |
| Han et al[19]             | Six-week open label pharmacological study with task related fMRI acquisition    | n = 19; Males 100%        | SCID                                     | Task used: Cue-reactivity paradigm. Task design: Videogame viewing Behavioral results: Gaming craving: IGD > NC | Scanner: 1.5 T                        | At baseline:                                                                                     |
|                           | Aim: To evaluate the efficacy of bupropion SR in reducing game craving and influencing brain activity in IGD | Medication free (at study enter) 100% | BDI < 17                                 | fMRI scan duration: 7.5 min Acquisition method: Block design Software used: Brain voyager       |                                       |                                                                                  |
|                           |                                  | Normal neurological      | 7 point Gaming Craving VAS               |                                                                                                 |                                       |                                                                                  |
|                           |                                  | examination 100%          |                                          |                                                                                                 |                                       |                                                                                  |
|                           |                                  | No comorbid psychiatric disorders or substance use                            |                                          |                                                                                                 |                                       |                                                                                  |
| Dong et al[20]            | Task related fMRI study                                                        | n = 27; Males 100%        | MINI                                     | Task used: Guessing task Task design: Two-choices gain or loss guessing task Behavioral results: No between group significant differences in accuracy and reaction times For NC: YIAT < 20 | Scanner: 3 T                          | Between group significant effects: (1) In WIN condition: IGD > NC in L occipital lobe, cuneus, L DLPFC, L PH After 6 wk of Bupropion treatment on IGD: |
|                           | Aim: To investigate reward and punishment processing in IGD during a guessing task | Medication free 100%     |                                          |                                                                                                 |                                      |                                                                                  |
|                           |                                  | Right-handed 100%         |                                          |                                                                                                 |                                      |                                                                                  |
|                           |                                  | Normal neurological      |                                          |                                                                                                 |                                      |                                                                                  |
|                           |                                  | examination 100%          |                                          |                                                                                                 |                                      |                                                                                  |
|                           |                                  | No comorbid psychiatric disorders or substance use                            |                                          |                                                                                                 |                                      |                                                                                  |
|                           |                                  | Groups: IGD n = 11        |                                          |                                                                                                 |                                      |                                                                                  |
|                           |                                  | Mean age: 22.7 ± 1.3 yr   |                                          |                                                                                                 |                                      |                                                                                  |
|                           |                                  | Mean age: 21.5 ± 5.6 yr   |                                          |                                                                                                 |                                      |                                                                                  |
|                           | Study treatment: Bupropion SR for 6 wk                                           | n = 8                      |                                          |                                                                                                 |                                      |                                                                                  |
|                           |                                  | Study treatment: Bupropion SR for 6 wk                                           | n = 8                      |                                                                                                 |                                      |                                                                                  |

Table 2 Task related functional magnetic resonance imaging studies on internet addiction disorder
### Dong et al.[22]

**Task related fMRI study**

**Aim:** To identify the neural correlates of response inhibition in individuals with and without IGD

**Groups:** IGD n = 14  
Mean age: 23.4 ± 3.3 yr  
NC n = 13  
Mean age: 24.1 ± 3.2 yr

For all participants:  
BDI < 13  
Task used: Cognitive control task  
Task design: Three-choices color-word Stroop task  
Behavioral results: No between group significant differences

**fMRI scan duration:** 12 min  
**Acquisition method:** Event-related design  
**Software used:** SPM5

**Between group significant effects:**  
IGD > HC in: ACC, PCC, L insula, MFG, MFG, L thalamus, R IFG, R SFG

**Task design:** Three-choices color-word Stroop task  
**Stimulus class:** No comorbid psychiatric disorders or substance use disorders  
**Non smokers:** 100%  
**Groups:** IGD n = 24;  
Males 100%  
Medication free 100%  
Right-handed 100%

**Signal analyzed:** BOLD  
**Whole brain analysis**

**Spending most of their time playing online Internet games**

**BIS 11**  
**Iowa Gambling test**  
**Grüsser and Thalemann’s criteria for computer game addiction**

**Behavioral results:**  
**Connectivity analysis:** Post hoc PPI, using R IFG as seed region

**Software used:** SPM8

**During incorrect responses:** IGD > NC in ACC

**Behavioral results:**  
**Software used:** SPM8

**During correct responses:** IGD > NC in ACC

---

### Lorenz et al.[23]

**Task related fMRI study**

**Aim:** To assess neural correlates of attentional bias and cue reactivity in IGD

**Groups:** IGD n = 12  
Mean age: 23.6 ± 3.5 yr  
NC n = 12  
Mean age: 24.2 ± 3.1 yr

**Task design:** Two-choice dot probe paradigm during SP and LP trials  
**fMRI scan duration:** 30 min

**Acquisition method:** Block design

**Behavioral results:**  
**Connectivity analysis:** Post hoc PPI, using R IFG as seed region

**Software used:** SPM8b

**During SP trials**

**Mean age:** 25 ± 7.4 yr  
**Vocabulary test (WST-IQ)**

**Test of attention**

**Behavioral results:**  
**Connectivity analysis:** Post hoc PPI, using R IFG as seed region

**Software used:** SPM8b

**During LP trials IGD > NC in:**  
R IFG, R Hippocampus, bilateral lingual gyrus and R calcaneus gyrus

**Behavioral results:**  
**Whole brain analysis**

**Signal analyzed:** BOLD

**Between group significant effects**

**Behavioral results:**  
**Whole brain analysis**

**Signal analyzed:** BOLD

**Between group significant effects**

**Behavioral results:**  
**Whole brain analysis**

**Signal analyzed:** BOLD

**Between group significant effects**

**Behavioral results:**  
**Whole brain analysis**

**Signal analyzed:** BOLD

**Between group significant effects**

**Behavioral results:**  
**Whole brain analysis**

**Signal analyzed:** BOLD

**Between group significant effects**

**Behavioral results:**  
**Whole brain analysis**

**Signal analyzed:** BOLD

**Between group significant effects**

---

### Sepede G et al.

**Neuroimaging of internet addiction**
| Author(s) | Task related fMRI study | Aim: To investigate brain correlates of decision-making in IAD | No comorbid psychiatric disorders or substance use disorders | For NC: YIAT < 30 | Group effects | Signal analyzed: BOLD | Whole brain analysis |
|---------|-------------------------|-------------------------------------------------|--------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Dong et al. | Task related fMRI study | MINI | Task used: Guessing task | Task design: Two-choice gain or loss guessing task | Behavioral results: | Scanner: 3 T | Between group significant effects |
| | | | | | | fMRI scan duration: 21 min | In WIN condition: IAD > NC in: ACC, insula and IFG |
| | | | | | | | IAD < NC in: PCC and caudatum |
| Dong et al. | Task related fMRI study | MINI | Task used: Guessing task | Task design: Two-choice gain or loss guessing task | Behavioral results: | Scanner: 3 T | Between group significant effects |
| | | | | | | fMRI scan duration: 21 min | In LOSS condition: IAD > NC in: ACC, insula and IFG |
| | | | | | | | IAD < NC in: PCC and caudatum |

| Author(s) | Task related fMRI study | Aim: To explore cognitive flexibility in IGD during a color-word Stroop task | | | | | |
|---------|-------------------------|-------------------------------------------------|--------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Dong et al. | Task related fMRI study | MINI | Task used: Cognitive control task | Task design: Three-choice color-word Stroop task | Focus: Cognitive flexibility during task switching (from easy to difficult condition and viceversa) | Scanner: 3 T | Between group significant effects |
| | | | | | fMRI scan duration: 16 min | Task switching |
| | | | | | | | (1) From difficult to easy condition |

| Author(s) | Task related fMRI study | Aim: To investigate reward/punishment sensitivities in IGD during a guessing task | No comorbid psychiatric disorders or substance use disorders | For NC: YIAT < 30 | Group effects | Signal analyzed: BOLD | Whole brain analysis |
|---------|-------------------------|-------------------------------------------------|--------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Dong et al. | Task related fMRI study | MINI | Task used: Guessing task | Task design: Two-choice gain or loss guessing task | Behavioral results: | Scanner: 3 T | Between group significant effects |
| | | | | | | fMRI scan duration: 21 min | In WIN condition: IAD > NC in: ACC, insula and IFG |
| | | | | | | | IAD < NC in: PCC and caudatum |
| Dong et al. | Task related fMRI study | MINI | Task used: Guessing task | Task design: Two-choice gain or loss guessing task | Behavioral results: | Scanner: 3 T | Between group significant effects |
| | | | | | | fMRI scan duration: 21 min | In LOSS condition: IAD > NC in: ACC, insula and IFG |
| | | | | | | | IAD < NC in: PCC and caudatum |
| Sepede G et al. | Neuroimaging of internet addiction | | | | | | |
| Study | Task/FMRI study | Participants | Details | Imaging Analysis | Between Group Significant Conditions |
|-------|----------------|--------------|---------|-----------------|---------------------------------------|
| Ko et al. | Task related fMRI study | Groups: IGD n = 15, NC n = 15 | Mean age: 21.2 ± 3.2 yr | For NC: YIAT < 30 | Spent > 80% of their time online playing games | No significant between group differences | Software used: SPM5 | IGD > NC in: Bilateral insula, R STG |
| Liu et al. | Task related fMRI study | Groups: IGD n = 26, NC n = 23 | Mean age: 24.4 ± 3.2 yr | For IGD: Fulfilling DCIA criteria | No comorbid psychiatric disorders or substance use disorders | Software used: SPM5 | During error processing |
| Chen et al. | Task related fMRI study | Groups: IGD n = 11, NC n = 11 | Mean age: 22.4 ± 1.7 yr | For NC: FTND < 5 | No comorbid psychiatric disorders or substance use disorders | Software used: SPM5 | During gaming distracting condition |

**Behavioral results:**
- No significant between group differences
- No significant between group differences
- No significant between group differences
conditions can be analyzed, to evaluate reward and punishment neural systems\(^1\).

In cognitive control tasks, participants have to choose between different conflicting responses. Stimuli can be manipulated to increase difficulty and to measure particular cognitive abilities, such as sustained attention, response inhibition, impulsivity, task switching ability and error processing. Frequently used cognitive control tasks are the Stroop tasks: Participants are required to detect only a salient characteristic of the stimuli, ignoring the others (i.e., color words printed in different colored ink and participants have to ignore the word and name its color)\(^2\). When the different features of the stimuli are incongruent, the task difficulty increases and affects...
the performance (Stroop effect)\(^\text{[43]}\). Another important category of control tasks is the “go no-go paradigm”: Stimuli (i.e., digits, letters, shapes) are presented in a continuous stream and participants perform a binary decision on each stimulus. One of the outcomes requires participants to make a motor response (go), whereas the other requires participants to withhold a response (no-go)\(^\text{[44]}\).

When the study is focused on the influence of emotion or salience on selective attention, dot prob paradigms are frequently used: Participants view neutral or salient stimuli appearing randomly on either side of the screen, then a dot is presented in the location of one former stimulus and participants have to indicate the correct location of the dot, so an attentional bias toward salient stimuli can be detected\(^\text{[45,46]}\).

**Cue-reactivity task fMRI studies in IAD**

In their study on 10 IGDp addicted to the videogame World of Warcraft (WOW) Ko et al\(^\text{[47]}\) found that IGDp reported a higher gaming urge when passive viewing WOW images with respect to NC. Moreover, a significant higher activation was observed in right orbitofrontal cortex, right basal ganglia (caudatum and accumbens), bilateral anterior cingulate cortex, bilateral medial prefrontal cortex, right dorsolateral prefrontal cortex.

Han et al\(^\text{[48]}\) conducted a six-week open label pharmacological study aiming to evaluate bupropion efficacy in reducing game craving and modulate brain activation in 11 IGDp addicted to the videogame Starcraft. At baseline, all participants were medicated free and the authors observed an higher game urge and an augmented activation of left dorsolateral prefrontal cortex, L parahippocampus, left occipital lobe and cuneus in IGDp, with respect to NC during Starcraft cue presentation. After bupropion treatment, a significant decreased activation of left dorsolateral prefrontal cortex was observed in IGDp. Bupropion, being an antidepressant agent modulating dopamine and norepinephrine reuptake, was reported to be efficacious in patients with substance use disorder, with or without comorbid mood disorders\(^\text{[47,48]}\) and in pathological gambling\(^\text{[49]}\). So the authors hypothesized that bupropion reduced craving in IGD by modulating dorsolateral prefrontal cortex functional activity.

In a recent study using videogame stimuli, Liu et al\(^\text{[43]}\) (2015) enrolled a mixed-gender sample of 19 IGDp (males 58%) and reported a significant dysfunction of the frontal cortex, with increased activation in right-sided temporoparietal and limbic regions: Superior parietal lobe, insula, cingulate gyrus and superior temporal gyrus.

**Guessing task fMRI studies in IAD**

To evaluate reward and punishment sensitivity in IGDp, Dong et al\(^\text{[20]}\) simulated a gain/loss situation: Participants had to choose between two covered playing cards and at the end of the fMRI scan session they received a money sum based on their wins and losses. fMRI data analysis revealed that during win condition IGDs showed an higher activation of left orbitofrontal cortex (BA11) with respect to NC, whereas in loss condition the opposite was true for anterior cingulate cortex activation. So the authors concluded that a reduced sensitivity to negative experiences (monetary loss) and an augmented sensitivity to positive events (monetary gain) throughout an altered functioning of orbitofrontal cortex and anterior cingulate cortex could explain why IADp persisted in their habit despite the negative consequences on their everyday life.

Using a similar guessing task, Dong et al\(^\text{[25]}\) found that IGDp were significantly slower than NC when exposed to continuous losses, whereas no behavioral group effects were observed after continuous wins. In terms of brain activations, IGDs showed a reduced activation of posterior cingulate cortex and an increased activation of inferior frontal gyrus during both win and loss conditions, whereas an augmented activation of anterior cingulate cortex and insula was observed during win condition only. These results suggested that decision-making ability was impaired in IGDp, due to a functional inefficiency in the inferior frontal gyrus (higher activation but lower behavioral performance) and a reduced involvement of posterior cingulate cortex and caudate. In the same study sample, with a modified guessing paradigm (a different control condition was added to wins and losses) Dong et al\(^\text{[26]}\) asked the participants to describe their subjective experience after the scan section: IGDp reported higher craving for win in both continuous win and loss conditions and reduced negative emotions during loss conditions. In terms of functional activations, the results were similar, but not identical to those previously reported\(^\text{[25]}\) (probably due to the different control condition): IGDp hyperactivated the left superior frontal gyrus in both wins and losses (but the level of activation was higher during wins) and hypoactivated the posterior cingulate cortex during losses. The authors concluded that superior frontal gyrus in IGDp was insensitive to negative situations and posterior cingulate cortex failed to exert its cognitive control on environmental changes.

**Cognitive control task fMRI studies in IAD**

In the eight cognitive controls fMRI studies we selected, Stroop tasks were used in four studies\(^\text{[22,24,27,31]}\), go/no-go paradigms in three studies\(^\text{[28,30]}\) and a dot/prob paradigm in one study\(^\text{[23]}\).

Dong et al\(^\text{[22]}\) enrolled 12 male, drug free and non-smokers IGDp and compared them with healthy peers during a three-choices color-word Stroop task. The groups did not differ in terms of behavioral performance, but during Stroop effect (incongruent - congruent stimuli contrast) IGDp showed a significant hyperactivation in anterior cingulate cortex, posterior cingulate cortex, left insula, middle frontal gyrus, medial frontal gyrus, left thalamus, right inferior frontal gyrus, right superior frontal gyrus.

The authors speculated that a greater activation of
posterior cingulate cortex in IGD group could indicate a failure to optimize task related attentional resources due to an incomplete disengagement of Default Mode Network. Furthermore, the hyperactivation of the anterior cingulate cortex, insula and prefrontal regions might reflect a cognitive inefficiency of fronto-limbic regions playing a key role in conflict monitoring and “top down” inhibitory control.

In a larger sample, Dong et al. administered the same Stroop paradigm with an event-related design and separately analyzed the functional correlates of correct and error responses to stimuli. IGDp and NC performed similarly, but differences emerged in activation patterns: during correct responses IGDP failed to activate anterior cingulate cortex and orbitofrontal cortex, whereas an abnormal activation of anterior cingulate cortex was observed during errors, thus suggesting an impaired error monitoring ability.

More recently, Dong et al. analyzed the cognitive flexibility of a group of IGD during a modified version of the Stroop task, adding a monetary reward for correct responses and creating easy and difficult task conditions. The two group did not significantly differ behaviorally. On the other hand, when the task switched from difficult to easy condition IGDP activated the bilateral insula and right superior temporal gyrus more than NC; when the task switched from easy to difficult condition, they hyperactivated the bilateral precuneus, left superior temporal gyrus and left angular gyrus. The authors hypothesized that an higher (and therefore less efficient) activation of limbic and temporoparietal regions playing a key role in inhibitory control and cognitive flexibility was a biomarker of IGD.

The same inhibitory control impairment was found in another study by Dong et al. As a part of a larger resting state connectivity study, a subsample of IGDs performed a Stroop task during an event related fMRI scanning. The authors observed that during incongruent trials, IGDs showed an augmented activation of bilateral superior frontal gyrus and a reduced activation of left dorsolateral prefrontal cortex, left orbitofrontal cortex and anterior cingulate cortex, all regions implicated in executive control.

Ko et al. used a go/no-go paradigm with digit stimuli to assess response inhibition and error processing in 26 male IGDP. The authors did not found significant behavioral deficits in IGDP, with respect to NC. On the contrary, when analyzing fMRI data, they reported significant group effects: During successful response inhibition, IGDP activated the bilateral caudate and left orbitofrontal gyrus more than NC; during error commission they failed to activate the right insula. Orbitofrontal gyrus and insula are key regions in modulating inhibitory control and error processing, so the authors suggested that IGDP needed to hyperactivate the orbitofrontal gyrus to successfully perform the task and compensate for the insular hypofunction.

In a recent article, Chen et al. used a block design to analyze the functional correlates of cognitive control in IGDP by means of a short go/no-go task. Even though behaviorally intact, IGDP showed a reduced activation of supplementary motor area/pre supplementary motor area, a key region in selecting the appropriate behavior, withholding wrong responses.

Liu et al. enrolled a mixed gender sample of IGDP and used a modified go/no-go paradigm, entering gaming picture as background distracters. They observed similar group performance in the original paradigm, but more commission errors during the cue distraction condition in the IGD group. Moreover, during the original task, IGDP hyperactivated the right superior parietal lobe, whereas during the gaming distracting condition they hypoactivated the right dorsolateral prefrontal cortex, right superior parietal lobe and cerebellum. A Region of Interest based analysis revealed that in IGDP the rate of commission errors was positively associated with the right dorsolateral prefrontal cortex and right superior parietal lobe activation. The authors therefore suggested that gaming cues significantly affected inhibitory control in IGDP, throughout a failure of dorsolateral prefrontal cortex and superior parietal lobe function.

A cognitive task with emotional and cue distracters was also used by Lorenz et al. in a small group of IGDP: They administered a two-choice dot probe paradigm during short (SP) and long presentation (LP) trials in order to elicit attentional bias and cue reactivity, respectively. Stimuli were International Affective Picture System based emotional images (with neutral or positive valence) and computer generated images (neutral pictures or images based on World of Warcraft videogame). IGDP showed a significant attentional bias vs both game related and affective pictures with positive valence. Compared to NC, IGDP showed an abnormal activation of medial prefrontal cortex, anterior cingulate cortex, left orbitofrontal cortex and amygdala during SP trials and of occipital regions, right inferior frontal gyrus and right hippocampus during LP trials. In authors’ opinion, IGDP patients showed a behavioral and neural response similar to that observed in patients with substance use disorder, giving more attention to positive stimuli.

DISCUSSION

In this paper we systematically reviewed the resting state and task related fMRI studies on adult patients with IAD. All but one of the papers included in our qualitative synthesis were conducted in the Asian continent, confirming the great attention given to this potential harmful condition by Eastern governments.

The majority of the studies were conducted on young male IGDP (mean age ≤ 25 years), with only a few females and subjects with non-gaming Internet addiction. To avoid any confounding effects of other conditions, we included only studies conducted in subjects free of any comorbid psychiatric or substance use disorder.

Summarizing the literature findings, we highlighted...
that IGDp differed from healthy comparisons in the functioning of several brain regions involved in reward and executive control/attention processing, even when they were behaviorally intact.

In particular, the most reported cortical dysfunctions were located in orbitofrontal gyrus, anterior cingulate cortex, insula, dorsolateral prefrontal cortex, superior temporal gyrus, inferior frontal gyrus, precuneus and posterior cingulate cortex, whereas for subcortical regions, functional alterations were often found in brainstem and caudate.

Orbitofrontal cortex is involved in decision-making, value-guided behaviors and reward/punishment sensitivity\cite{51,52}. Through its multiple connections with prefrontal, limbic and sensorial regions, it estimates the potential reward of a given stimulus and the appropriate behavior in order to achieve a positive outcome. In patients with substance addiction, an altered functioning of orbitofrontal cortex has been linked to craving and impaired decision-making\cite{53}. Anterior cingulate cortex and insular cortex are both relevant in sustained attention, conflict monitoring, error signaling\cite{54} and processing of unpleasant stimuli\cite{55}. They provide a hub between different cerebral systems, binding emotion to cognition\cite{56,57}. Altered functioning of anterior cingulate cortex and insula have been found in alcohol and drug addiction\cite{58,59}.

Dorsolateral prefrontal cortex is a region involved in different cognitive tasks, such as working memory\cite{60} and motor skill learning\cite{61}. An abnormal activation of dorsolateral prefrontal cortex was found in heavy alcohol drinkers with respect to light drinkers during a go/no go task\cite{62}, and in pathological gamblers during a cue-reactivity task\cite{63}.

Superior temporal gyrus was found activated in the processing of audiovisual stimuli with an emotional context\cite{64} and during task shifting\cite{65}. A reduced activation of superior temporal gyrus was reported in cocaine addicts during a Stroop task\cite{66}.

Inferior frontal gyrus has a role in cognitive inhibition\cite{67}, target detection\cite{68}, decision making\cite{69} and emotional processing\cite{70}. In response to decision-making involving uncertainty and during aversive interoceptive processing, young adults with problematic use of cocaine and amphetamine exhibited a reduced inferior frontal gyrus activation with respect to both former stimulant users and healthy controls\cite{71}. The precuneus has a pivotal role in self-consciousness, visuo-spatial imagery, episodic memory retrieval\cite{72} and target detection during high difficulty tasks\cite{73}. In their work on internet addicts, Ko et al\cite{74} reported an increased activation of precuneus during game cue exposure in acutely ill IGDp, but not in remitted IGD.

Posterior cingulate cortex is considered part of the default mode of the brain\cite{75}, and its deactivation during high demanding cognitive tasks is seen as an expression of a reallocation of processing resources\cite{76}. An altered function of posterior cingulate cortex and other components of Default Mode Network was reported in cocaine addicts, especially in those with chronic use\cite{77}.

The importance of brainstem in providing ascending and descending pathways between brain and body is well documented\cite{78}. In particular, prefrontal regions and anterior cingulate cortex are deeply connected to the brainstem, so a dysfunction of this subcortical structure leads to attentional and executive impairments\cite{79}.

Caudate nucleus is involved in posture, motor control and modulation of approach/attachment behavior\cite{80}. In response to alcohol cues, heavy alcohol users showed higher caudate activation with respect to moderate users\cite{81}.

Radiological imaging is a useful research strategy in psychiatric and neurological fields, and may be considered as a form of “molecular pathological epidemiology”\cite{82,83}, an interdisciplinary research area aiming to investigate the complex relationships among genes, environment, molecular alterations and long term outcome of clinical disorders\cite{84}.

Taken together, the results of our systematic review suggest that young adult with IGD, without any other psychiatric disorder, showed a pattern of functional brain alterations similar to those observed in substance addiction.

Altered functioning of anterior and posterior cingulate cortex, prefrontal and parietal regions, limbic areas and subcortical structures results in impaired response inhibition and abnormal sensitivity to reward and punishment. As observed in substance use disorders, patients with IAD show a reduced cognitive flexibility, more stereotyped responses and inappropriate behavior, with negative consequences on social and working life\cite{85-87}.

**Limits of the study**

The majority of patients enrolled in the reviewed studies were males IGDp, so the conclusions can’t be extended to other subtypes of IAD or to female patients. Focusing our review on adult subjects, we excluded fMRI studies conducted on pediatric and adolescent populations.

**COMMENTS**

**Background**

Internet addiction disorder (IAD) is an impulse control disorder characterized by an uncontrolled Internet use, associated with a significant functional impairment or clinical distress. Even if it is not classified as a mental disorder in the current edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), it is a highly debated condition, due to its relevant prevalence among adolescents and young adults.

**Research frontiers**

Some of the clinical characteristics of IAD, such as loss of control, craving and withdrawal symptoms when patients are not allowed to use the Internet are similar to those observed in behavioral or substance use disorders. Therefore, in the last years several neuroimaging studies have been conducted aiming to investigate the relation between the clinical presentation of IAD and the functioning of cortical and subcortical regions involved in reward processing and cognitive control.
Innovations and breakthroughs
Neuroimaging research is nowadays a promising approach to fill the gap between the molecular basis of psychiatric disorders and their clinical manifestations. The scientific literature on debated diagnosis such as IAD is rapidly growing, so providing an updated review of the last published data may be of interest for the readers. Focusing the authors‘ systematic review on homogeneous study samples (only adult patients, no psychiatric comorbid conditions allowed) results of different researches can be easily compared to find similarities and discrepancies.

Applications
In clinical settings, patients with the same psychiatric condition often differ from one another in terms of clinical symptoms, response to pharmacological treatments and long-term outcome. Studying their brains and behaviors in details could help to provide more accurate diagnosis and treatments.

Terminology
IAD: An impulse control disorder characterized by an uncontrolled Internet use, associated with a significant functional impairment or clinical distress; IGD: A subtype of IAD, also called videogame addiction, characterized by excessive online gaming as the principal Internet activity.

Peer-review
This is a very interesting article.

REFERENCES
1 Young KS. Internet addiction: the emergence of a new clinical disorder. *Cyberpsychol Behav* 1998; 1: 237-244 [DOI: 10.1089/ cyph.1998.1.237]
2 American Psychiatric Association (APA) Diagnostic and statistical manual of mental disorders (5th ed). Washington, DC, 2013. Available from: URL: http://www.psychiatry.org/
3 Cheng C, Li AY. Internet addiction prevalence and quality of (real) life: a meta-analysis of 31 nations across seven world regions. *Cyberpsychol Behav Soc Nerv 2014; 17: 755-760* [PMID: 25489876 DOI: 10.1089/cyber.2014.0317]
4 Krishnamurthy S, Chetlapalli SK. Internet addiction: Prevalence and risk factors: A cross-sectional study among college students in Bengaluru, the Silicon Valley of India. *Indian J Public Health 2015; 59: 115-121* [PMID: 26021648 DOI: 10.4103/0019-557X.15 7531]
5 Rumpf HJ, Vermulst AA, Bischof A, Kastirke N, Gürtler D, Bischof G, Meerkerk GJ, John U, Meyer C. Occurrence of internet addiction in a general population sample: a latent class analysis. *Addict Res Dev 2014; 20: 159-166* [PMID: 24401314 DOI: 10.1159/000354321]
6 Choi SW, Kim HS, Kim GY, Jeon Y, Park SM, Lee JY, Jung HY, Sohn BK, Choi JS, Kim DJ. Similarities and differences among Internet gaming disorder, gaming disorder and alcohol use disorder: a focus on impulsivity and compulsivity. *J Behav Addict 2014; 3: 246-253* [PMID: 25592310 DOI: 10.1556/JBA.3.2014.4.6]
7 Bipeta R, Yerramilli SS, Karredla AR, Gopinath S. Diagnostic Stability of Internet Addiction in Obsessive-compulsive Disorder: Data from a Naturalistic One-year Treatment Study. *Innov Clin Neurosci 2015; 12: 14-23* [PMID: 26600291]
8 Wöllfling K, Beutel ME, Dreier M, Müller KW. Bipolar spectrum disorders in a clinical sample of patients with Internet addiction: hidden comorbidity or differential diagnosis? *J Behav Addict 2015; 4: 101-105* [PMID: 26132914 DOI: 10.1556/2006.4.2015.011]
9 Tonioni F, Mazza M, Autillo G, Cappelluti R, Catalano V, Marano G, Fiumana V, Moschetti C, Alimonti F, Luciani M, Lai C. Is Internet addiction a psychopathological condition distinct from pathological gambling? *Addict Behav 2014; 39: 1052-1056* [PMID: 24630825 DOI: 10.1016/j.addbeh.2014.02.016]
10 Walton E, Turner JA, Ehrlich S. Neuroimaging as a potential biomarker to optimize psychiatric research and treatment. *Int Rev Psychiatry 2013; 25: 619-631* [PMID: 24151806 DOI: 10.3109/09 540261.2013.816659]
11 Bullmore E. The future of functional MRI in clinical medicine. *Neuroimage 2012; 62: 1267-1271* [PMID: 22261574 DOI: 10.1016/ j.neuroimage.2012.01.026]
12 Mitscherlichfield MT, Ettinger U, Mehta MA, Mataix-Cols D, Williams SC. Applications of functional magnetic resonance imaging in psychiatry. *J Magn Reson Imaging 2006; 23: 851-861* [PMID: 16652410]
13 van den Heuvel MP, Hulshoff Poel HE. Exploring the brain network: a review on resting-state fMRI functional connectivity. *Eur Neuropsychopharmacol 2010; 20: 519-534* [PMID: 20471808 DOI: 10.1016/j.euroneuro.2010.03.008]
14 Sava S, Yurgelun-Todd DA. Functional magnetic resonance in psychiatry. *Top Magn Reson Imaging 2008; 19: 71-79* [PMID: 19363430 DOI: 10.1097/RMR.0b013e318184187c]
15 Greicius M. Resting-state functional connectivity in neuropsychiatric disorders. *Curr Opin Neurol 2008; 21: 424-430* [PMID: 18607202 DOI: 10.1097/ WCO.0b013e328306f625]
16 Honey GD, Fletcher PC, Bullmore ET. Functional brain mapping of psychopathology. *J Neurol Neurosurg Psychiatry 2002; 72: 432-439* [PMID: 11909899]
17 Ko CH, Liu GC, Hsiao S, Yen JY, Yang MJ, Lin WC, Yen CF, Chen CS. Brain activities associated with gaming urge of online gaming addiction. *J Psychiatr Res 2009; 43: 739-747* [PMID: 18996542 DOI: 10.1016/j.jpsychires.2008.09.012]
18 Liu J, Gao XP, Osunde I, Li X, Zhou SK, Zheng HR, Li LJ. Increased regional homogeneity in internet addiction disorder: a resting state functional magnetic resonance imaging study. *Chin Med J (Engl) 2010; 123: 1904-1908* [PMID: 20819576]
19 Han DH, Hwang JW, Renshaw PF. Bupropion sustained release treatment decreases craving for video games and cue-induced brain activity in patients with Internet video game addiction. *Exp Clin Psychopharmacol 2010; 18: 297-304* [PMID: 20695685 DOI: 10.1037/a0020023]
20 Dong G, Huang J, Du X. Enhanced reward sensitivity and decreased loss sensitivity in Internet addicts: an fMRI study during a guessing task. *J Psychiatr Res 2011; 45: 1525-1529* [PMID: 21764067 DOI: 10.1016/j.jpsychires.2011.06.017]
21 Dong G, Huang J, Du X. Alterations in regional homogeneity of resting-state brain activity in internet addicts. *Behav Brain Func 2012; 8: 41* [PMID: 22901705 DOI: 10.1186/1744-9081-8-41]
22 Dong G, Devito EE, Du X, Cui Z. Impaired inhibitory control in ‘internet addiction disorder’: a functional magnetic resonance imaging study. *Psychiatry Res 2012; 203: 153-158* [PMID: 22892351 DOI: 10.1016/j.psychres.2012.02.001]
23 Lorenz RC, Krüger JK, Neumann B, Schott BH, Kaufmann C, Heinz A, Wüstenberg T. Cue reactivity and its inhibition in pathological computer-gaming players. *Addict Biol 2013; 18: 134-146* [PMID: 22970898 DOI: 10.1111/j.1369-1600.2012.00491.x]
24 Dong G, Shen Y, Huang J, Du X. Impaired error-monitoring function in people with Internet addiction disorder: an event-related fMRI study. *Eur Addict Res 2013; 19: 269-275* [PMID: 23548798 DOI: 10.1159/000346783]
25 Dong G, Hu Y, Lin X, Lu Q. What makes Internet addicts continue playing online even when faced by severe negative consequences? Possible explanations from an fMRI study. *Biol Psychol 2013; 94: 282-289* [PMID: 23933447 DOI: 10.1016/j.biopsycho.2013.07.009]
26 Dong G, Hu Y, Lin X. Reward/punishment sensibilities among internet addicts: Implications for their addictive behaviors. *Prog Neuropsychopharmacol Biol Psychiatry 2014; 43: 139-145* [PMID: 23876789 DOI: 10.1016/j.pnpbp.2013.07.007]
27 Dong G, Lin X, Zhou H, Lu Q. Cognitive flexibility in internet addicts: fMRI evidence from difficult-to-easy and easy-to-difficult switching situations. *Addict Behav 2014; 39: 677-683* [PMID: 24368005 DOI: 10.1016/j.addbeh.2013.11.028]
28 Ko CH, Hsieh TJ, Chen CY, Yen CF, Chen CS, Yen JY, Wang PW, Liu GC. Altered brain activation during response inhibition and error processing in subjects with Internet gaming disorder: a functional magnetic imaging study. *Eur Arch Psychiatry Clin Neurosci 2014; 264: 661-672* [PMID: 24460909 DOI: 10.1007/
29 Liu GC, Yen JY, Chen CY, Chen CS, Lin WC, Ko CH. Brain activation for response inhibition under gaming cue distraction in internet gaming disorder. *Ko 2014; 39: 43-51 [PMID: 24380858 DOI: 10.1016/j.kjms.2013.08.005]

30 Chen CY, Huang MF, Yen JY, Chen CS, Liu GC, Yen CF, Ko CH. Brain correlates of response inhibition in Internet gaming disorder. *Psychiatry Clin Neurosci* 2015; 69: 201-209 [PMID: 25047685 DOI: 10.1111/pcn.12224]

31 Dong G, Lin X, Potenza MN. Decreased functional connectivity in an executive control network is related to impaired executive function in Internet gaming disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2015; 60: 104-111 [PMID: 25609820 DOI: 10.1016/j.pnpbp.2015.02.004]

32 Liu J, Li W, Zhou S, Zhang L, Wang Z, Zhang Y, Jiang Y, Li L. Functional characteristics of the brain in college students with internet gaming disorder. *Brain Imaging Behav* 2015; Epub ahead of print [PMID: 25763841]

33 Zhang JT, Yao YW, Li CS, Zang YF, Shen ZJ, Liu L, Wang LJ, Liu B, Fang XY. Altered resting-state functional connectivity of the insula in young adults with Internet gaming disorder. *Addict Biol* 2015; Epub ahead of print [PMID: 25899520 DOI: 10.1111/adb.12247]

34 Beard KW, Wolf EM. Modification in the proposed diagnostic criteria for Internet addiction. *Cyberpsychol Behav* 2001; 4: 377-383 [PMID: 11702626]

35 Ko CH, Yen JY, Chen SH, Yang MJ, Lin HC, Yen CF. Proposed diagnostic criteria and the screening and diagnosing tool of Internet addiction. *J Clin Psychiatry* 2006; 67: 1050-1056 [PMID: 16712334]

36 Grüsser SM, Thalamenschn. VS. Verhaltenssucht: Diagnostik, Therapie, Forschung. Bern: Huber, 2006

37 Franken HI. Drug craving and addiction: integrating psychological and neuropsychopharmacological approaches. *Prog Neuropsychopharmacol Biol Psychiatry* 2003; 27: 563-579 [PMID: 12787841]

38 Wilson SJ, Sayette MA, Fiez JF. Prefrontal responses to drug cues: a neurocognitive analysis. *Nat Neurosci* 2004; 7: 211-214 [PMID: 15001989]

39 Reuter J, Raedler T, Rose M, Hand I, Gläscher J, Büchel C. Pathological gambling is linked to reduced activation of the mesolimbic reward system. *Nat Neurosci* 2005; 8: 147-148 [PMID: 15643429]

40 MacLeod CM. Half a century of research on the Stroop effect: an integrative review. *Psychol Bull* 1991; 109: 163-203 [PMID: 2034749]

41 Stroop JR. Studies of interference in serial verbal reactions. *J Exp Psychol* 1935; 18: 643-662 [DOI: 10.1037/h0054651]

42 Hester R, Fassbender C, Garavan H. Individual differences in error processing: a review and reanalysis of three event-related fMRI studies using the Go/NoGo task. *Cereb Cortex* 2004; 14: 986-994 [PMID: 15115734]

43 Bradley B, Field M, Mogk K, De Houwer J. Attentional and evaluative biases for smoking cues in nicotine dependence: component processes of biases in visual orienting. *Behav Pharmacol* 2004; 15: 29-36 [PMID: 15075624]

44 MacLeod C, Mathews A, Tata P. Attentional bias in emotional disorders. *J Abnorm Psychol* 1986; 95: 15-20 [PMID: 3700842]

45 Castells X, Casas M, Pérez-Mañá C, Roncerro C, Vidal X, Capellà D. Efficacy of psychostimulant drugs for cocaine dependence. *Cochrane Database Syst Rev* 2010; (2): CD007380 [PMID: 20166094]

46 Sepede G, Di Iorio G, Lupi M, Sarchione F, Acciaiati T, Fiori F, Santacroce R, Martinotti G, Gambi F, Di Giannantonio M. Bupropion as an add-on therapy in depressed bipolar disorder type 1 patients with comorbid cocaine dependence. *Clin Neuropharmacol* 2014; 37: 17-21 [PMID: 24434527 DOI: 10.1097/ WNF.0000000000000111]

47 Dannon PN, Lowengrub K, Musin E, Gonopolski Y, Kolter M. Sustained-release bupropion versus naltrexone in the treatment of pathological gambling: a preliminary blind-rater study. *J Clin Psychopharmacol* 2005; 25: 593-596 [PMID: 16282845]

48 Ahn DH. Korean policy on treatment and rehabilitation for adolescents’ Internet addiction in 2007 International Symposium on the Counseling and Treatment of Youth Internet Addiction. Seoul, Korea, National Youth Commission, 2007: 49

49 Rangel A, Camerer C, Montague PR. A framework for studying the neurobiology of value-based decision making. *Nat Rev Neurosci* 2008; 9: 545-556 [PMID: 18545266]

50 Rolls ET, Grabenhorst F. The orbitofrontal cortex and beyond: from affect to decision-making. *Prog Neurobiol* 2008; 86: 216-244 [PMID: 18824074 DOI: 10.1016/j.pneurobio.2008.09.00]

51 London ED, Ernst M, Grant S, Bonson K, Weinstein A. Orbitofrontal cortex and human drug abuse: functional imaging. *Cereb Cortex* 2000; 10: 334-342 [PMID: 10731228]

52 Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci* 2000; 4: 215-222 [PMID: 10827444]

53 Petrovic P, Pleger B, Seymour B, Klöppel S, De Martino B, Critchley H, Dolan RJ. Blocking central opiate function modulates hedonic impact and anterior cingulate response to rewards and losses. *J Neurosci* 2008; 28: 10509-10516 [PMID: 18933027]

54 Kühn S, Gallinat J. Common biology of craving across legal and illegal drugs - a quantitative meta-analysis of cue-reactivity brain response. *Eur J Neurosci* 2011; 33: 1318-1326 [PMID: 21261758]

55 Kurth F, Zilles K, Fox PT, Laird AR, Eickhoff SB. A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. *Brain Struct Funct* 2010; 214: 519-534 [PMID: 20512376 DOI: 10.1007/s00429-010-0255-z]

56 Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am J Psychiatry* 2002; 159: 1642-1652 [PMID: 12359667]

57 Schacht JP, Anton RF, Myrick H. Functional neuroimaging studies of alcohol cue reactivity: a quantitative meta-analysis and systematic review. *Addict Biol* 2013; 18: 121-133 [PMID: 22546861 DOI: 10.1111/j.1369-1600.2012.00464.x]

58 Petrides M. The role of the mid-dorsolateral prefrontal cortex in working memory. *Exp Brain Res* 2000; 133: 44-54 [PMID: 10933209]

59 Seidler RD, Bo J, Anguera JA. Neurocognitive contributions to motor skill learning: the role of working memory. *J Mot Behav* 2012; 44: 445-453 [PMID: 23237467 DOI: 10.1080/00222895.2012.672348]

60 Ames SL, Wong SW, Bechara A, Cappelli C, Dust M, Grenard JL, Stacy AW. Neural correlates of a Go/NoGo task with alcohol stimuli in light and heavy young drinkers. *Behav Brain Res* 2014; 274: 382-389 [PMID: 25172182 DOI: 10.1016/j.bbr.2014.08.039]

61 Crockford DN, Goodyear B, Edwards J, Quickfall J, el-Guebaly N. Cued-induced brain activity in pathological gamblers. *Biol Psychiatry* 2005; 58: 787-795 [PMID: 15993856]

62 Robins DL, Hungsdit S, Schultz RT. Superior temporal activation in response to dynamic audio-visual emotional cues. *Brain Cogn* 2009; 69: 269-278 [PMID: 18809234]

63 Buchsbaum BR, Greer S, Chang WL, Berman KF. Meta-analysis of neuroimaging studies of the Wisconsin card-sorting task and component processes. *Hum Brain Mapp* 2005; 25: 35-45 [PMID: 15846821]

64 Barrós-Loscertales A, Bastamante JC, Ventura-Campos N, Llopis JJ, Pareat MA, Avila C. Lower activation in the right frontoparietal
network during a counting Stroop task in a cocaine-dependent group. Psychiatry Res 2011; 194: 111-118 [PMID: 21958514 DOI: 10.1016/j.psychres.2011.05.001]

67 Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex. Trends Cogn Sci 2004; 8: 170-177 [PMID: 15050513]

68 Mantini D, Corbetta M, Perrucci MG, Romani GL, Del Gratta C. Large-scale brain networks account for sustained and transient activity during target detection. Neuroimage 2009; 44: 265-274 [PMID: 18793734]

69 Reckless GE, Ousdal OT, Server A, Walter H, Andreassen OA, Farde L, Lochhead P, Chan AT, Nishihara R, Cho E, Wolpin B, Cavanna AE. Anatomy of the brainstem: evidence from a partial correlation network analysis. Front Syst Neurosci 2013; 7: 89 [PMID: 24298242 DOI: 10.3389/ fssys.2013.00089]

70 Frühholz S, Grandjean D. Processing of emotional vocalizations in bilateral inferior frontal cortex. Neurosci Biobehav Rev 2013; 37: 2847-2855 [PMID: 24161466 DOI: 10.1016/j.neubiorev.2013.10.007]

71 Stewart JL, Parnass JM, May AC, Davenport PW, Paulus MP. Altered frontocingulate activation during aversive interoceptive processing in young adults transitioning to problem stimulant use. Neurosci Biobehav Rev 2013; 37: 4689-4699 [PMID: 21036793 DOI: 10.1136/gut.2010.217182]

72 Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. Brain 2006; 129: 564-583 [PMID: 16399806]

73 Astafiev SV, Shulman GL, Stanley CM, Snyder AZ, Van Essen DC, Corbetta M. Functional organization of human intraparietal and frontal cortex for attending, looking, and pointing. J Neurosci 2003; 23: 4689-4699 [PMID: 12805308]

74 Ko CH, Liu GC, Yen JY, Chen CY, Yen CF, Chen CS. Brain correlates of craving for online gaming under cue exposure in subjects with Internet gaming addiction and in remitted subjects. Addict Biol 2013; 18: 559-569 [PMID: 22026537 DOI: 10.1111/j.1369-1600.2011.00405.x]

75 Fransson P, Marrelec G. The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: Evidence from a partial correlation network analysis. Neuroimage 2008; 42: 1178-1184 [PMID: 18598773]

76 McKiernan KA, Kaufman JN, Kucera-Thompson J, Binder JR. A parametric manipulation of factors affecting task-induced deactivation in functional neuroimaging. J Cogn Neurosci 2003; 15: 394-408 [PMID: 12729491]

77 Konova AB, Moeller SJ, Tomasi D, Goldstein RZ. Effects of chronic and acute stimulants on brain functional connectivity hubs. Brain Res 2015; 1628: 147-156 [PMID: 25721787 DOI: 10.1016/j.brainres.2015.02.002]

78 Angeles Fernández-Gil M, Palacios-Bote R, Leo-Barahona M, Mora-Encinas JP. Anatomy of the brainstem: a gaze into the stem of life. Semin Ultrasound CT MR 2010; 31: 196-219 [PMID: 20483389]

79 Hurley RA, Flashman LA, Chow TW, Taber KH. The brainstem: anatomy, assessment, and clinical syndromes. J Neuropsychiatry Clin Neurosci 2010; 22: iv, 1-7 [PMID: 20160204]

80 Villablanca JA. Why do we have a caudate nucleus? Acta Neurobiol Exp (Wars) 2010; 70: 95-105 [PMID: 20407491]

81 Dager AD, Anderson BM, Rosen R, Khadka S, Sawyer B, Jiantonio-Kelly RE, Austad CS, Raskin SA, Tennen H, Wood RM, Fallahi CR, Pearlson GD. Functional magnetic resonance imaging (fMRI) response to alcohol pictures predicts subsequent transition to heavy drinking in college students. Addiction 2014; 109: 585-595 [PMID: 24304235 DOI: 10.1111/add.12437]

82 Ogino S, Chan AT, Fuchs CS, Giovannucci E. Molecular pathological epidemiology of colorectal neoplasia: an emerging transdisciplinary and interdisciplinary field. Gut 2011; 60: 397-411 [PMID: 21036793 DOI: 10.1136/gut.2010.217182]

83 Nishi A, Kawachi I, Koenen KC, Wu K, Nishihara R, Ogino S. Lifecourse epidemiology and molecular pathological epidemiology. Am J Prev Med 2015; 48: 116-119 [PMID: 25528613 DOI: 10.1016/j.amepre.2014.09.031]

84 Ogino S, Lochhead P, Chan AT, Nishihara R, Cho E, Wolpin BM, Meyerhardt JA, Meissner A, Schernhammer ES, Fuchs CS, Giovannucci E. Molecular pathological epidemiology of epigenetics: emerging integrative science to analyze environment, host, and disease. Mod Pathol 2013; 26: 465-484 [PMID: 23307060 DOI: 10.1038/modpathol.2012.214]

85 Lundqvist T. Imaging cognitive deficits in drug abuse. Curr Top Behav Neurosci 2010; 3: 247-275 [PMID: 21161756 DOI: 10.1007/7854_2009_26]

86 Luijten M, Machiels MW, Veltman DJ, Hester R, de Haan L, Franken IH. Systematic review of ERP and fMRI studies investigating inhibitory control and error processing in people with substance dependence and behavioural addictions. J Psychiatry Neurosci 2014; 39: 149-169 [PMID: 24359877]

87 Zhu Y, Zhang H, Tian M. Molecular and functional imaging of internet addiction. Biomed Res Int 2015; 2015: 378675 [PMID: 25879023 DOI: 10.1155/2015/378675]
