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Resting-State Abnormalities in Heroin-Dependent Individuals

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Abstract

Drug addiction is a major health problem worldwide. Recent neuroimaging studies have shed light into the underlying mechanisms of drug addiction as well as its consequences to the human brain. The most vulnerable, to heroin addiction, brain regions have been reported to be specific regions in the prefrontal, parietal, occipital, and temporal lobes, as well as, some subcortical regions.The brain regions involvedare linked with reward, motivation/drive, memory/learning, inhibition as well as emotional control andseem to form circuitsthat interact with each other. So, along with neuroimaging studies, recent advances in resting-state dynamics might allow further assessments upon the multilayer complexity of addiction. In the current manuscript, we comprehensively reviewand discuss all the existing resting-state neuroimaging findings classified into three overlapping and interconnected groups: functional connectivity alterations, structural deficits and abnormal topological properties. Moreover, behavioral traits of heroin-addicted individuals as well as the limitations of the currently available studies are also reviewed. Finally, in need of a contemporary therapya multimodal therapeutic approach is suggested using classical treatment practices along with current neurotechonologies, such as neurofeedback and goal-oriented video-games

Keywords:Heroin addiction, resting-state, functional and structural connectivity, small-world properties, behavioral traits of heroin-dependent individuals.

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Abbreviations

Nucleus Accumbens (NAc)

Orbitofrontal Cortex (OFC)

Anterior Cingulate Cortex (ACC)

Resting-state Functional Connectivity (rsFC)

Blood Oxygen Level-Dependent (BOLD)

Default-Mode Network (DMN)

Structural Connectivity (SC)

Amplitude of Low-Frequency Fluctuation (ALFF)

Diffusion Tensor Imaging (DTI)

Fractional Anisotropy (FA)

Independent Component Analysis (ICA)

Discrete Cosine Transform (DCT)

Functional Magnetic Resonance (fMRI)

Ventral part of ACC (vACC)

Ventral Medial Prefrontal Cortex (vmPFC)

Posterior Cingulate Cortex/ precuneus (PCC/pC)

Medial Prefrontal Cortex (MPFC)

Dorsolateral Prefrontal Cortex (DLPFC)

Rostral aspect of ACC (rACC)

Dorsal aspect of ACC (dACC)

Inferior Parietal Lobe (IPL)

Pharmacological MRI (phMRI)

Gray Matter (GM)

Cingulate Cortex (CC)

White Matter (WM)

Radial Diffusivity ($\lambda^{\perp}$)

Axial Diffusivity ($\lambda_{\parallel}$)

Inferior Longitudinal Fasciculus (ILF)

Superior Longitudinal Fasciculus (SLF)

Apparent Diffusion Coefficient (ADC)

Resting Cerebral Blood Flow (rCBF)

ROI-approach (Region of Interest – approach)

Graph theory analysis (GTA)

Supramarginal Motor Area (SMA)

Iowa Gambling Test (IGT)

Delay-Discounting Task (DDT)

Polysubstance users (PSA)

Frontal System Behavior Scale (FrSBe)

Point Subtraction Aggression Paradigm (PSAP)

Prefrontal cortex (PFC)

Ventral Tegmental Area (VTA)

Degree (D)

Brain-Computer Interface (BCI)

Heroin-Dependent (HD)

Cognitive Normal (CN)

Opiate Dependent (OD)

Prolonged Abstinent(PA)

Heroin Group(HG)

Placebo Group (PG)

Brain Dopamine System (DA)

Inferior Frontal Gyrus (IFG)

Inferior Parietal Lobule (IPL)

Cingulate Gyrus(CG)

Middle Cingulate Gyrus(MCC)

Parahippocampal Gyrus(PHG)

Supplementary Motor Cortex(SMC)

Fusiform Area(FFA)

Medial Frontal Gyrus (MeFG)

Cerebellar Peduncles(MCP)

Intrinsic Amygdala Functional Network(iAFC)

Fagerstrom Test of Nicotine Dependence(FTND)

Total Incranial Fluid (TIV)

Cerebrospinal Fluid(CSF)

Radial Diffusivity(RD)

Drug addiction or substance dependence(Koob and Le Moal, 2005)is defined as a multifaceted neuropsychiatric disorder resulting from complex interactions between neurobiological, environmental, genetic and pharmacological variables(Sutherland et al., 2012).It affects both cognitive as well as emotional processes(Zhang et al., 2013). Furthermore, the compulsive seeking and taking of the drug despite the negative consequences, (including downward social mobility(Denier et al., 2013b)), constitutes its behavioral phenotype(Volkow et al., 2003). According to Everitt and Robbins (2013), drug addiction could be also defined as the final phase of a series of adjustments from voluntary use, to habitual and gradually to compulsive behavior that is not easily reversed.

Numerous studies have discussed the underlying mechanism of drug addiction(Goldstein and Nora D. Volkow, 2002; Redish, 2004; Kalivas and Volkow, 2005; Koob and Le Moal, 2008; Wise, 2008). The addiction's model proposed by Volkow et al. (2003) consists of four interacting and overlapping circuits: the reward circuit, which located in the ventral pallidum and the nucleus accumbens (NAc), the motivation/drive circuit, which is represented by the orbitofrontal cortex (OFC) and the subcallosal cortex, the memory/learning circuit, which is located in the hippocampus and the amygdala and finally control circuit, which islocated in the anterior cingulate cortex (ACC) and the prefrontal cortex. A typical addicted brain is characterized by an overactivation in the reward, the motivation/drive as well as the memory/learning circuits that it is motivated by the enhanced drug's value and results in inhibitory control overcoming(Volkow et al., 2003) (see Figure 1). This feedback-loop is initiated by the drug consumption and is maintained by the overactivation of both motivation/drive and memory/learning circuits(Volkow et al., 2003). Heroin addiction has been also involved in the modulation of behavioral traits (Zeng et al., 2013), that is probably induced by the absence of bidirectional interactions between reward-control and motivation/drive-control circuits (see Figure 1).

[Figure 1]

Recently the scientific community has witnessed an explosion in the study of functional connectivity modulations(Polunina et al., 2007; Ma et al., 2010, 2011; Wang et al., 2010, 2013; Yuan et al., 2010a; Jiang et al., 2011; Xie et al., 2011; Zhang et al., 2011; Moreno-López et al., 2012), structural deficits(Liu et al., 2008, 2009a; Yuan et al., 2009, 2010b; Bora et al., 2010; Wang et al., 2012; Qiu et al., 2011, 2013; Wang et al., 2011; Lin et al., 2012; Denier et al., 2013a; Zhang et al., 2013; Li et al., 2013a, 2013c) and changes in topological properties(Liu et al., 2009b, 2011; Yuan et al., 2010c; Jiang et al., 2013) in heroin-dependent individuals at rest.Resting-state is defined as a state that is characterized by the absence of a specific goal-oriented activity or alternatively as a task-free state where the subjects rest quietly awake with their eyes closed, as it has been proposed by Raichle et al. (2001). Nevertheless, a more complex baseline or control state such as visual fixation of a cross hair on a monitor or alternatively passive viewing of a stimulus(Greicius et al., 2003; Fox et al., 2005; Fransson, 2006; Fair et al., 2008; Fransson and Marrelec, 2008) is more frequently used.

In fMRI, the resting-state functional connectivity (rsFC) is an examination of correlations in low-frequency (<0.1 Hz)(Cordes et al., 2000) or (<0.08 Hz) (Halbout et al., 2011) spontaneous fluctuations in the blood oxygen level-dependent (BOLD) signal. Although the intrinsic functional connectivity and neuronal populations' interaction(Honey et al., 2009) are presumed to be reflected by these temporal correlations(Greicius et al., 2009), the origin of the observed synchrony remains obscure(Fox et al., 2005).

A set of brain regions functionally connected is referred to as a "functional network"(Honey et al., 2009). Biswal et al. (1995) first demonstrated that primary sensorimotor areas' brain activity was functionally connected across the hemispheres at rest. Furthermore, identical behavior at resting-state is presented by several brain systems such as the auditory, the visual and the language processing networks(Biswal et al., 1995; Lowe et al., 1998; Hampson et al., 2002; Van de Ven et al., 2004; Fox et al., 2005). Moreover, up to ten cortico-cortical and subcortical resting-state networks have been reported by Beckmann et al. (2005) and Damoiseaux et al. (2006). Surprisingly, the persistence of these resting-state networks is overt during both sleep(Fukunaga et al., 2006; Honey et al., 2009) and anesthesia(Fox et al., 2005; Vincent et al., 2007).

One such network called the default-mode network (DMN) or task-negative network(Fox et al., 2005;Fox and Greicius, 2010) has been extensively studied and has also been used as a potential diagnostic tool in neuropathological disorders(He et al., 2007; Greicius, 2008). DMN is a set of brain regions initially detected by Shulman et al. (1994), including posterior cingulate, the medial prefrontal and the medial and lateral parietal cortex. The DMN, is activated during resting-state and deactivated during cognitive process. Greicius et al. (2003)reported that this network is minimally disrupted during sensory tasks with limited cognitive demand. The DMN is associated with "introspective" and "self-referential" mental activity(Gusnard et al., 2001), "mentalizing"(Frith and Frith, 1999, 2003), "autobiographical" self(Gusnard et al., 2001; Buckner and Carroll, 2007), "self-projection"(Buckner and Carroll, 2007), "stimulus independent thought"(Gusnard et al., 2001; Mason et al., 2007), episodic memory(Greicius et al., 2003; Shannon and Buckner, 2004). Furthermore, it is involved in drug-addiction(Wang et al., 2010; Ma et al., 2011; Li et al., 2013b). Fox et al. (2005) proposed that the DMN, as well as another set of brain regions called the task-positive network organize the human brain. These two distinct functional networks are not only functionally anticorrelated but they are also dynamically interacting and coexisting(Fox et al., 2005; Fransson, 2006).

Greicius et al. (2009) and Honey et al. (2009) studied the relationship between resting-state functional connectivity (rsFC) and structural connectivity (SC) of the human brain from different aspects. Greicius et al. (2009) suggested that functional connectivity reflects to a large degree structural connectivity but there does not exist a one-to-one equivalence. Honey et al. (2009) confirmed the absence of a one-to-one mapping between the two connectivity types and evaluated the role of brain regions' distance in connectivity patterns.

Recent resting-state imaging studies have revealed that the human brain is organized in highly clustered sub-networks with a small characteristic path. These findings imply that functionally interregional connectivity is characterized by small world topology(Van den Heuvel et al., 2008). Consequently, both resting-state functional and structural connectivity as well as small-world topology compose a global description of brain's function at rest. Furthermore, resting-state connectivity provides reliable, quick and straightforward data collection when studying populations with variable attentional, motor and executive control(Sutherland et al., 2012). It enables

the detection of underlying neuronal circuitry dysfunctions in numerous neurological disorders including autism(Kennedy et al., 2006), Alzheimer's disease(Lustig et al., 2003; Greicius et al., 2004; Rombouts et al., 2005; Wang et al., 2006), depression(Anand et al., 2005), attention and hyperactive disorders(Tian et al., 2006) and multiple sclerosis(Lowe et al., 2002).Thus, resting-state connectivity can serve both as a biomarker of neurological diseases, as well as a helpful diagnostic tool(Sutherland et al., 2012). Furthermore, resting state networks are consistent across time within and between the subjects(Chen et al., 2008) and can be used as predictor of stimulus related neural responses(Wang et al., 2013). Last but not least,Glahn et al. (2010) and Meyer-Lindenberg (2009) suggested the existence of a genetic association between resting-state functional networks and behavior.

The current manuscript is a comprehensive review of the available knowledge on alterations in resting-state networks, induced byheroin addiction (Table 1in the Appendix A provides a complete list of studies considered in this review). The currently available information on heroin-dependents individuals is classified into three overlapping categories: functional connectivity alterations, structural deficits and abnormal topological small-world properties. A discussion on both behavioral traits of heroin-addicted individuals and the role of the different brain regions affected by heroin addiction is also included. Finally, the correlation between heroin induced alterations and the duration of heroin abuse as well as the limitations of recent resting-state imaging studies are discussed highlighting scientific areas for further investigation.

Methodology

Published studies have been identified through the Google Scholar database for the period from 2006 to 2015. The main keywords and phrases used have been "heroin addiction", "resting-state alterations in heroin addiction", "abnormalities induced by heroin addiction", "functional connectivity in heroin addicts", "structural deficits in heroin-dependent individuals", "small world properties in heroin addiction". Furthermore, lists of references from the studies considered have been also searched. Only articles in English language wereconsidered. Finally, articles, abstracts, book chapters, as well as, studies that have been published in nonpeer-reviewed journals have not been used.

The collected studies have been divided into three sections: resting-state functional alterations, structural deficits and abnormal topological small-world properties of heroin-dependent individuals. The keywords used in order to classify the studies according to aforementioned design have been: "resting-state functional connectivity (rsFC)", "functional connectivity", "amplitude of low-frequency fluctuation (ALFF)", "accuracy" for the first section. The words and phrases "gray matter", "gray matter volume", "gray matter density", "white matter", "white matter integrity"," diffusion tensor imaging (DTI) values", "axonal diffusivity", "radial diffusivity", "fractional anisotropy (FA)", "cerebral perfusion", "brain regional homogeneity", "cortical thickness" for the second section. Finally, we used studies with terminology such as "characteristic path length", "clustering coefficient", "density", "small-world metric", "global efficiency", "local efficiency", "hub", "degree" that is commonly used inthe analysis of brain networks based on graph theory.

Resting-State Functional Connectivity Alterations in Heroin Individuals

The brain regions that are the most vulnerable to heroin dysfunctions are the prefrontal, parietal, occipital, and temporal regions, as well as, the subcortical regions that satisfy Volkow et al.'s (2003) model.

Numerous computational techniques have been used until today in order to assess the functional connectivity in heroin-dependent individuals. These include the pattern classification technique(Zhang et al., 2011), the seed-based(Ma et al., 2010; Wang et al., 2013) or ROI seed-based(Wang et al., 2010; Li et al., 2013b) correlation analysis, the independent component analysis (ICA)(Ma et al., 2011), the voxel-based analysis(Moreno-López et al., 2012), the amplitude of low-frequency fluctuation(Jiang et al., 2011; Wang et al., 2013) and the discrete cosine transform (DCT)(Yuan et al., 2010a). Furthermore, most of imaging studies on functional connectivity have been conducted with functional Magnetic Resonance (fMRI).

Despite the increasing scientific interest in functional connectivity alterations in heroin addiction the currently available data are controversial. An earlier investigation(Polunina et al., 2007) claimed that the electric activityespecially in central brain regions of heroin-addicts is influenced shortly after the onset of intoxication. In particular, these changes are initially observed in the left hemisphere and very soon spread to the central part of the right hemisphere(Polunina et al., 2007).

Ma et al. (2010) studied chronic heroin users and compared them with a control group of healthy individuals. They reported stronger rsFC between nucleus accumbens (NAc) and both ventral/rostral aspect of anterior cingulate cortex (ACC) and medial orbitofrontal cortex (OFC) as well as between lateral OFC and amygdala compared to controls. Moreover, higherrsFC was also detected between lateral and medial aspect of OFC as well as within the OFC of chronic heroin users' brain relatively to controls(Ma et al., 2010). The opposite findings were found when the medial-dorsolateral aspect of prefrontal cortex was compared with the lateralOFC as well as the dorsal ACC. In addition, diminished rsFC was found in addicted group compared to controls within the lateral OFC, between OFC and several frontal and parietal regions as well as between the dorsal and the ventral/rostral part of ACC(Ma et al., 2010).

The same group, Ma et al. (2011) in a more recent study conducted on the same population group as before, reported an abnormal functional organization of the DMN. More precisely, heroin users exhibited stronger rsFC within theDMN in the right hippocampus but weaker in the right dorsal aspect of ACC and the left caudate. Opposite findings were reported by Wang et al. (2010)who suggested a decreased functional connectivity in heroin users compared to control group between the ventral part of ACC (vACC) and the right NAc and a significant functional connectivity between the vACC and the bilateral medial prefrontal cortex (MPFC) of heroin abusers. A weaker functional phenotype was reported between the vACC and the rightthalamus, the bilateral posterior cingulate cortex/ precuneus (PCC/pC), the rightparahippocampal gyrus/amygdala and the ACC bilaterally(Wang et al., 2010). However,a significant rsFCwas found between the vACC and the left inferior and middle temporal gyrus, the left transverse temporal gyrus as well as the insula, the ACC, the superior temporal gyrus and the OFC/MPFC all bilaterally in heroin abusers(Wang et al., 2010).

Another resting-state imaging study(Yuan et al., 2010a)reported that heroin-dependent subjects showed significantrsFC between posterior cingulate cortex/precuneus (PCC/ pC) and both bilateral angular gyrus and

middle temporal lobe as well as the right dorsolateral prefrontal cortex (DLPFC). Nevertheless, a reduced rsFC compared to the healthy group was found in heroin addicts between posterior cingulate cortex/precuneus (PCC/ pC) and both left DLPFC and right cerebellum(Yuan et al., 2010a). In the same study(Yuan et al., 2010a) the rostral aspect of ACC (rACC) showed a weak rsFC with several brain regions such as the left OFC, the right middle temporal lobe and the left DLPFC. It is crucial to mention that PCC/ pC and rACC have not showed enhanced connectivity in the group of heroin-dependent individuals according to the aforementioned study. This finding contradicts to the findings ofWang et al. 2010 who reported significant functional connectivity between ventral aspects of anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC)/ medial PFC. Finally, Yuan et al. (2010) reported that a distributed brain network that is involved in drug addiction and consists of ACC, amygdala, OFC, DLPFC, NAc, MPFC and insula according to the existing literature(Wilson et al., 2004; Lee et al., 2005; Fu et al., 2008; Yuan et al., 2009). Another study(Yuan et al., 2010b) of the same research group revealed a reduced rsFC between the right DLPFC and the left inferior parietal lobe (IPL).

Furthermore, Zhang et al. (2011) compared abstinent heroin-dependents individuals with a control group of healthy individuals and reported differences in the OFC, thepara-limbic and frontal brain regions, the cingulate gyrus, the posterior insula and the thalamus.Another fMRI study evaluated the association between the resting-state intrinsic amygdala network of abstinent heroin addicts and their impulsive behavior(Xie et al., 2011). In accordance with Yuan et al. (2010) and Ma et al. (2010), the aforementioned study concluded that the amygdala showed significant rsFC with the PCC/pC and the OFC respectively. In addition, there were several brain regions bearing the same characteristic that belong to the temporal system as well as the subcortical regions(Xie et al., 2011). On the other hand, the amygdala showedanticorrelations with brain regions located in the prefrontal, occipital and parietal system(Xie et al., 2011).

More recently, Wang et al. (2013) measured the amplitude of low frequency fluctuation (ALFF) in heroin-dependent individuals and compared it with that of healthy controls. They detected dysfunctions of the fronto-cerebellum and the fronto-striatal circuits that influence the balance between local neuronal activity and the network's organization and might result gradually from voluntary to compulsive drug use. More precisely, enhanced rsFC was showed between the caudate and the cerebellum on the right hemisphere as well as between the right dACC and the right inferior parietal and lingual gyrus(Wang et al., 2013). Similar findings were detected between dACC and bilateral inferior frontal gyrus as well as the left superior frontal, temporal and posterior frontal gyrus, the right medial frontal gyrus and the middle temporal gyrus bilaterally(Wang et al., 2013). However, reduced rsFC was detected between right caudate and right superior temporal and frontal gyrus, left angular gurus as well as middle frontal gyrus bilaterally(Wang et al., 2013). In addition, they reported increased ALFF in the left superior temporal and occipital gyrus as well as in the cerebellum bilaterally. However, diminished ALFF relative to controls was detected in caudate, dACC and superior medial frontal cortex of the right hemisphere(Wang et al., 2013). Applying the same computational tool, Jiang et al. (2011)detected increased ALFF in the bilateral angular and the supramarginal gyrus, the PCC/precuneus bilaterally and the left middle frontal gyrus. Instead, reduced ALFF was reported in the dACC and the middle OFC bilaterally, the PCC, the DLPFC, the middle and inferior temporal gyrus as well as the cuneus in the left hemisphere. Consistent with the study of Wang et al. (2013), they reported ALFF changes in subcortical and cortical brain regions but however the brain regions were not identical (see Figure 2) (Wang et al., 2013).

Moreover, Li et al. (2013) highlighted the key-role of PCC/pC and reported its stronger rsFC with the insula and dorsal striatum bilaterally, the right inferior parietal lobe (IPL) and the supramarginal gyrus in heroin addicts compared to thecontrol group. Moreover, they suggested that the PCC-insula and PCC-striatum dysfunctions may be regarded as biomarkers of the severity of damage induced by heroin. A more recent study indicated the existence of a connected subnetwork that presented significantly altered in the heroin group compared to the control group(Jiang et al., 2013).

Since the loss of volitional controlover drug-taking behaviorsand the desire for immediate reward constitute a distinguishingfeature of drug addiction, many researchers proposed different brain networks that might influence the decision processes.This increased impulsivity has been attributed to a weak top-down of executive networks combined with hypersensitivity of reward networks(Lawrence et al., 2009; Peters and Büchel, 2011; Limbrick-Oldfield et al., 2013). More precisely, a single-valuation model has been proposed (Kable and Glimcher, 2007, 2009) including OFC, ventral medial PFC and striatum. McClure et al. (2004, 2007) extended the existing knowledge proposing a dual-valuation model. They defined theβ-network that mediates for short-term rewards including OFC, striatum and ventral medial PFC and theδ-network involving parietal and lateral prefrontal cortices that mediates for long-term rewards.Recent studies proposed that executive network modulates the valuation network (Figner et al., 2010; Baumgartner et al., 2011; Steinbeis et al., 2012; Bartra et al., 2013).

Xie et al. (2014), exploring the way that the two spatially separate and functionally distinct networks interact, found that the NAc was more strongly connected with the components of β-network in heroin-dependent individuals compared to controls. However, the NAc showed significantly decreased functional connectivity with the components of δ-network in heroin group relative to controls. Therefore, they concluded that β- and δ- networks are in imbalanced interaction in heroin-dependent individuals. In line with this finding, Zhai et al. (2015), using the ventral medial PFC as region of interest, reported that the rsFCbetween the vmPFC and the β-network's components including NAc, right medial OFC, caudate bilaterally and right PCC was higher in heroin-dependent group compared to control group. However, the rsFCbetween the vmPFC and the components of δ-network such as right IFG and IPL as well as the dorsal medial and dorsolateral PFC bilaterally was significantly lower in heroin-dependent individuals compared to controls. Additionally, they found the BIS-11 total score and the BIS III Motor Impulsivity subscalewere positively correlated to β-network connectivity and negatively associated with the δ-network's connectivity in heroin-dependent individuals.However, theNonplanning impulsivity subscale was positively associated with the components of δ-network in the control group. Finally, they concluded that both β- and δ- networks jointly influence the valuation neural processes modulating the behavioral impulsivity. Therefore, the decision-making processes and the impulsivity seem to be mutually influenced by both δ- and β-networks.

All theaforementioned, heroin-induced changes in the rsFC provide evidence that supports an abnormal functional organization of the brain in heroin addicted individuals(Yuan et al., 2010b).

Resting-State Structural Deficits in Heroin Dependent Individuals

Structural connections between brain regions wereinitially identified in nonhuman primates and particularly in macaques, by using tract-tracing techniques(Greicius et al., 2009). Similar methods are not applicable in humans

because antemortem injections are required to reach the most effective tracers. On the other hand, postmortem tracers have no practical value due to their glacial pace(Sparks et al., 2000). But, researchers are now equipped withmodern imaging technologies such as structural magnetic resonance(Liu et al., 2009a; Wang et al., 2012; Li et al., 2013a) or fMRI associated with voxel-based morphometry approach(Yuan et al., 2010b; Qiu et al., 2013), regional homogeneity tool(Qiu et al., 2011), pharmacological MRI (phMRI)(Denier et al., 2013a) or fMRI combined to a pulsed arterial spin labeling(Denier et al., 2013b) and quantitative diffusion tensor imaging(Liu et al., 2008; Bora et al., 2010; Wang et al., 2011; Lin et al., 2012; Zhang et al., 2013).

Numerous imaging studies have shown structural deficits that are associated both gray(Liu et al., 2009a; Yuan et al., 2009, 2010b; Wang et al., 2012; Denier et al., 2013a; Qiu et al., 2013) and white matter(Liu et al., 2008; Bora et al., 2010; Wang et al., 2011; Lin et al., 2012; Li et al., 2013c; Zhang et al., 2013) reductions, perfusion's decrement(Denier et al., 2013a, 2013b), diminished homogeneity(Qiu et al., 2011) and abnormal cortical thickness(Li et al., 2013a). Moreover, few studies associated structural reductions with rsFC impairments(Liu et al., 2009b; Yuan et al., 2009, 2010a, 2010c; Ma et al., 2010) despite the fact that their causal relationship remains unknown.

Gray Matter

According to a recent imaging study(Yuan et al., 2010b), heroin abstinent individuals presented significantly lowergray matter (GM) density in the right dorsolateral part of the prefrontal cortex (DLPFC) and fusiform gyrus and also in the left inferior parietal lobe and middle cingulate gyrus (CG) compared to the control group consistently with other studies(Lyoo et al., 2006; Yuan et al., 2009). Moreover, after a short period of abstinence decreased GM density was found not only in the frontal cortex as before but also in the occipital and cingulate regions(Wang et al., 2012). Although, after an abstinence period of one month several structural deficits subsided, nevertheless, GM impairments still remained in the right middle frontal gyrus and the left inferior occipital and cingulate gyrus indicating that heroin induced structural deficits are not a permanent, irreversible lesion(Wang et al., 2012). Yuan et al. (2009) further reinforced these results, by showing that heroin dependent individuals presented loss of GM density in the insula and the cerebellum(Yuan et al., 2009).

In addition to the above findings, it has been shown that heroin-dependent individuals exhibit GM volume atrophy in the right PFC, the cingulate cortices bilaterally and the left supplementary motor cortex(Liu et al., 2009a). Furthermore, Qiu et al. (2013) reported that heroin-dependent individuals showed decreased GM volume bilaterally in the MPFC including the ACC and the DLPFC as well as the right fusiform cortex that connects the occipital and temporal cortex. Similar findings were reported in an earlier study(Lyoo et al., 2006) on comorbid opiate-dependents individuals where GM volume disintegrationwas exhibited bilaterally in the PFC, the insula and the superior temporal cortex. In this study, GM atrophy was also found in the left fusiform cortex and the right uncus.

White Matter

Exposure to heroin has also been associated with white matter (WM) density impairments. According to Li et al. (2013), heroin-addicted individuals presented widespread WM density disruption in anterior and superior brain regions, compared to healthy controls. This research group used fractional anisotropy (FA) and the eigenvalues radial diffusivity($\lambda^\perp$) and axial diffusivity ($\lambda_\parallel$), and detected adecreased FA caused by enhanced $\lambda^\perp$ and stable $\lambda_\parallel$

in the bilateral frontal sub-gyrus, medial frontal and cingulate gyrus, right superior frontal gyrus, left temporal sub-gyral regions and posterior thalamus nucleus bilaterally. Furthermore, heroin individuals exhibited myelin damage which was proved based on the fact that radial diffusivity ($\lambda^\perp$) reflects the thickness of muelin sheets and their integrity(Song et al., 2002, 2005). Axial diffusivity ($\lambda_\parallel$) reflects axonal integrity and the fiber's structural organization(Song et al., 2002, 2005; Li et al., 2013c). When the genetic backround of heroin addicts was studied, it was reported that Met/Met homogygous subjects have an increased vulnerability to prefrontal WM density deficits that is enhanced by enviromental exposure to heroin(Zhang et al., 2013).

Lin et al. (2012) studied such WM density reductions in heroin-addicts under methadone treatment and identified them at temporal and frontal lobes, cerebellum, pons and cingulum bundles. As far as the type of heroin induced WM impairment is concerned, different results have been published until today. Reduced FA, increased radial but almost stable axonal diffusivity have been reported in left parahippocampus and cingulate gyrus and left inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF) and uncinate fasciculus as well as cerebellar peducles bilaterally indicating myelin injury(Song et al., 2002, 2005; Lin et al., 2012). On the contrary, reduced FA and axonal diffusivity but increased radial diffusivity have been reported in left uncinate and right inferior fronto-occipital fasciculus and cerebellum's anterior vermis(Lin et al., 2012). These phenomena might be linked to axonal and myelin damage or fiber deorganization(Song et al., 2002, 2005; Lin et al., 2012). The observed reduction in FAin heroin-dependent individuals under methadone treatment was further supported byBora et al. (2010) and Wang et al. (2011). Heroin-addicts under methadone treatment showed reduced FA in left genu but increased $\lambda^\perp$ and apparent diffusion coefficient (ADC) in corpus callosum's left splenium, compared to healthy individuals(Wang et al., 2011). On the other hand, heroin addicted individuals under methadone treatmentcompared to long-term abstinent heroin addicts presented an elevated ADC in corpus callosum's splenium bilaterally(Wang et al., 2011) providing evidence that WM's damage might occur during abstinence. In agreement with the aforementioned findings, it was reported that decreased FA with increased radial diffusivity was found in the corpus callosum, ILF and thalamus of opiate-dependent subjects(Bora et al., 2010). Likewise, another study showed a decrease in the FA in the left cingulate and right precentral gyrus and also bilateral frontal sub-gyrusof heroin addicts(Liu et al., 2008). However, prolonged heroin-dependent individuals showed reduced axial diffusivity in right frontal and superior longitudinal fasciculi, indicating that longer abstinence period could be linked to axonal injury in the aforestated brain regions(Bora et al., 2010).

Cerebral perfusion

Chronic heroin addiction is implicated in a global cerebral perfusion reduction, which is more evident inthe frontal, temporal and occipital lobes(Botelho et al., 2006). Denier et al. (2013a)reported that heroin induced hypoperfusion to left MPFC, insula bilaterally and right ACC. A negative correlation between heroin induced hypoperfusion and GM was also reported in bilateral inferior and temporal gyrus(Denier et al., 2013b). On the other hand, it was found that the acute effect of heroin involved hyperperfusion in the posterior cerebellar lobe, the left ACC and right precuneus(Denier et al., 2013a). Additionally, increased perfusion was observed in amygdalae(Denier et al., 2013a) eighty seconds after the intravenous admninistration of heroin whereas fifteen minutes after, enhanced perfusion was detected in the superior frontal gyrus of the left hemisphere (Kosel et al., 2008). Chronic heroin-dependents individuals who enrolled in a methadone maintenance program presented regional heterogeneity bilaterally located in themedial OFC, thalamus, cuneus and lingual gyrus(Qiu et al.,

2011). These findings are in agreement with the report of Pezawas et al. (2002)who found a decreased resting cerebral bood flow (rCBF) in the occipital cortex including the cuneus bilaterally whereas chronic opioid use mainly affected the prefrontal cortex.

Cortical thickness

Cortical thickness has been involved in various mental and pathological distortions(Dickerson et al., 2008; Li et al., 2013a) and might be a more effective measure than GM volume for brain's structure assessments(Hutton et al., 2009; Li et al., 2013a). Heroin dependence constitutes a disorder that might have a substantial effect on cortical thickness. More specifically, reduced cortical thickness has been observed in the bilateral superior frontal, the right superior temporal and insular and the left caudal middle frontal regions of heroin dependent individuals via a vertex-based approach(Li et al., 2013a). Partially overlaping regions have been identified through a ROI-approach in left superior frontal, calcarine and tranverse collateral sulcus and right lingual and occipital-temporal sulcus as well as in the left precuneus gyrus(Li et al., 2013a). Nonetheless, enhanced cortical thickness has been detected in the left superior parietal and temporal pole, right lateral occipital and inferior parietal regions as well as in the right cuneus and bilateral lingual gyrus using the vertex-based approach(Li et al., 2013a).

Abnormal Resting-State Topological Properties in Heroin-Dependents

Graph theory analysis (GTA) is a useful tool to investigate both neural dysregulations at rest as well as small-world properties of the brain(Liu et al., 2009b).Small-world organized networks are characterized by a high clustering coefficient which is indicative of a high sub-organization and a short path length that represents the communication efficiency(Watts and Strogatz, 1998; Sporns and Zwi, 2004). Small-world scalar represents the small-worldness and is defined as the ratio typically being greater than one(Liu et al., 2009b):

$$\delta = \frac{\gamma}{\lambda} = \frac{\frac{C_{net}}{C_{rand}}}{\frac{L_{net}}{L_{rand}}}$$

However, chronic heroin users showed a much smaller small-world scalar in diverse brain regions compare to healthy controls, presumably indicating the presence of distorted small-world properties(Liu et al., 2009b; Yuan et al., 2010c). Differences have also been detected in the degree of different brain regions between the two groups that is indicative of brain dysfunctions(Liu et al., 2009b). The degree of a vertex in a graph is defined as the number of the vertex's connections and it is used in order to assess the connectivity strength of a voxel with the others(Liu et al., 2009b). In heroin users an enhanced degree or connectivity strength, has been detected mainly in the supramarginal motor area (SMA) and the ACC but also in the amygdala, insula, hippocampus, putamen and pallidum, caudate, superior frontal gyrus' dorsolateral part and inferior orbito-frontal gyrus(Liu et al., 2009b). Another study that supported the former results, also included the bilateral OFC, precuneus, rostral part of ACC, cerebellum, putamen, parahippocampal gyrus and dorsolateral part of frontal cortex; thalamus, PCC, caudate, inferior and medial frontal cortex in the left hemisphere and right middle aspect of temporal gyrus as highly connected brain regions in heroin-dependent subjects(Yuan et al., 2010c) (see Figure 3). Additionally, Liu et al. (2011)investigated the abnormal topological properties in the parahippocampal and hippocampal

region, the PCC, the PFC, the ACC, the insula, the cerebellum, the thalamus, the amygdala, the temporal cortices and a significant part of the striatum (caudate, pallidum and putamen).

Chronic heroin dependence has been lately characterized as a disease that induces a whole-brain topological distortion(Jiang et al., 2013). Jiang et al. (2013) applying the GTA method in an improved way, suggested the global parameters clustering coefficient, global and local efficiency as well as the small-worldness and normalized clustering coefficient were found to be reducedin heroin addicts. However, the global parameters characteristic path length and normalized characteristic path length were enhanced in heroin-dependent individuals. On the other hand, nodal metrics such as the nodal degree (D_{nod}) and the nodal efficiency (E_{nod}) were lower in six brain regions (left middle frontal and inferior temporal gyrus, right thalamus and precuneus, middle dorsal aspect of cingulate gyrus bilaterally)(Jiang et al., 2013). The same nodal metrics were found to be higher in the left in inferior occipital and lingual gyrus and the hippocampus(Jiang et al., 2013). Furthermore, although eleven overlapping hub regions have been detected in both groups (heroin-dependent individuals and healthy controls), the left precuneus, right middle frontal and left postcentral gyrus have been specified in the heroin-dependent group whereas the left middle frontal gyrus, right precuneus and temporal pole have been highlighted in controls(Jiang et al., 2013).

[Insert Figure 3]

Behavioral Traits of Drug-Addicted Individuals

Heroin addiction,apart from widespread deficits in brain's function, structure and small-world topology, has alsobeen involvedin the modulation of behavioral traits(Zeng et al., 2013). Impulsivity, studied as a combination of decision-making ability and response inhibition(Zeng et al., 2013), constitutesone of the most common characteristics of heroin-addicted individuals. Li et al. (2013),used the Iowa Gambling Test (IGT) and the Delay-Discounting Task (DDT) in order to studydecision-making deficits and desire for immediate reward and found that abstinent heroin addicts exhibited poor performance in both tests, independent of abstinence length. Similar findings have been reported in previous studies on diverse substance abuse disorders(Watts and Strogatz, 1998; Sporns and Zwi, 2004; Honey et al., 2009). Furthermore, in another study, active heroin users showed diminished and risky decision-making, as well as longer consideration time relative to the control group(Fishbein et al., 2007; Li et al., 2013d). Similar findings have been reported in psychopathic abstinent heroin-addicted individuals when compared to their non-psychopathic counterparts(Vassileva et al., 2007; Li et al., 2013d). A previous study of Lee and Pau (2002) also confirmed the loss of inhibition control in abstinent heroin users. However, controversial findings have also been reported, such as those ofVerdejo-García, Perales, and Pérez-García (2007) who found poorer inhibition performance in polysubstance users (PSA) of cocaine,compared to PSA of heroin, whereas PSA of heroin showed no significant differences when compared to the healthy group.In a recent study, enhanced self-rated motor impulsive and experience-seeking behavioras well as partially cognitive impairment were reported in abstinent heroin individuals(Zeng et al., 2013). Moreover, a study between active and abstinent PSA (with an abstinence period of at least fifteen-days) showed poorer perfomance in DDT in heroin users, but not in alcoholics and cocaine-addicted individuals(Kirby and Petry, 2004). However, weakness in decision-making was not corroborated through IGT assessment,indicating that changes in decision-making might not survive after abstinence(Zeng et al., 2013).

A more recent study investigating the role of valuation networks, β- and δ-, in impulsive behaviors reported that the BIS-11 total score as well as all subscales were found to be higher in heroin-dependent group compared to controls(Zhai et al., 2015).The BIS-11 total score and the Motor Impulsivity subscale were positively associated with the β-network's connectivity but negatively correlated to δ-network's connectivity in heroin group. Moreover, Bechara (2005) reported that deficits in decision-making might precede substance addiction and may contribute to the maintenance and the progress to drug compulsive behavior. More precisely, the author challenged the old way of thinking that all people are equally susceptible to addiction once drugs become available. He argued that before getting to a stage in which brain changes are induced by a pattern of drug use, there is a decision that precedes the drug use and its progress to addiction. Thus, the decision-making mechanism protects people who experiment withdrugs from losing control and becoming progressively addicted. However, in some individuals the decision-making mechanism is dysfunctional due to genetic and/or environmental factors making individuals vulnerable to addiction. Furthermore, discussing about the affective pattern of drugs' negative consequences, he suggested that the affective pattern is represented in the brain when individuals learn about the dangers of drug use by parents or society.Although, the negative consequences of drug use are present and well-learned in the absence of the experimenting with drugs, poor decision-making induces "myopia" for the harmful effects facilitating the escalation from exposure to drug use and finally to compulsive intake.

In line with this, it is reported that a degree of structural abnormalities found in brain regions involved in decision-making might pre-exist promoting the progress from drug use to addiction. Additional evidence for the role of poor decision-making is provided by the exposure to drugs during adolescence. The development of prefrontal cortex functions as well as the neural connnections that undelie decision-making process is still in place until the age of 21(Crone et al., 2004; Overman et al., 2004). Therefore, exposure to drugs during adolescence could be harmful to the proper development of decision-making mechaning. However, it is needed more than a mere exposure to drugs to make an adolescent to be addicted. As such, he concluded that poor decision-making could more possibly be a predisposing factor for addiction rather than a product of drug use.

The moral aspect of decision-making is sacrificedbecause of utilitarian judgments of polysubstance abusers (including heroin consumption),concerning personal scenarios(Carmona-Perera et al., 2012). Additionally, these immoral choices are perceived without having any scruples(Carmona-Perera et al., 2012). Behavioral symptoms such as apathy, executive dysfunction and loss of inhibition were correlated with the severity of polysubstance addiction, but not uniformly across the variety of substances(Verdejo-García et al., 2006). Although use severity,for cocaine and ecstasy, was related to higher disinhibited behavior, acute doses of alcohol, cannabis and heroin were linked to higher scores in the apathy subscale of the Frontal System Behavior Scale (FrSBe)(Verdejo-García et al., 2006). Moreover, intensive use of alcohol and cannabis was involved in executive deficits(Verdejo-García et al., 2006).

Previous findings have also linked aggressive and violent behavior to the use of illicit substances, including cocaine, benzodiapezines, amphetamines and methamphetamines(Ben-Porath and Taylor, 2002; Boles and Miotto, 2003; Kuhns, 2005; Moore and Stuart, 2005). A recent study on aggressive behavior of adolescents who were enrolled in rehabilitation, showed that heroin and morphine had a positive correlation with the aggressive phenotype(Fauziah et al., 2012). Furthermore, adolescents reported moderate to high aggression levels in spite of their undergoing rehabilitation(Fauziah et al., 2012). Gerra et al. (2004)performed the Point Subtraction

Aggression Paradigm (PSAP) and reported that heroin-addicted individuals had higher aggressive responses relative to healthy participants. Furthermore, they did not find any significant correlation between the duration of heroin use and aggressiveness. However, they suggested that aggressive behavior might be attributed more to personality characteristics than to drug use(Gerra et al., 2004).

Social interactions modulate both behavioral traits and habits of substance use, according to the social influence theory(Dohrenwend et al., 1992). In other words, a network member observing the substance use by the other members has the tendency to mimic the friends' behavior(Reifman et al., 2006; Bohnert et al., 2009). A competing theory, called social selection theory,suggests that a drug-addicted person changes his social network in order to spend more time with other addicted individuals(Dohrenwend et al., 1992; Bohnert et al., 2009).Bohnert, Bradshaw and Latkin (2009) supported the bidirectional effect of the two aforementioned theories in the persistence of substance use behavior during adulthood. However, they reported that social selection is more crucial for adults and that it operates though short-term processes, whereas the closest peers do not have a stronger influence on drug-addicted adults,compared to their total social network(Bohnert et al., 2009). On the other hand, adults seem to be less vulnerable towards altering their attitude(Visser and Krosnick, 1998; Bohnert et al., 2009) and this might explain why the social influence needsmore time in order to have an effect on adult's drug use behavior(Bohnert et al., 2009). Moreover, social isolation constitutes a risk factor for substance use disorders(Volkow et al., 2011).

Substance use disorders were associated with the lack of insight into illness, as it also happens in various psychotic and mood disorders, as well as in obsessive-compulsive disorder(Husted, 1999; Pallanti et al., 1999; Pini et al., 2001; Dell'Osso et al., 2002; Marazziti et al., 2002; Varga et al., 2006; Verdejo-García and Pérez-García, 2008; Maremmani et al., 2012). Zeng et al. (2013) did not find any significant correlation between self-reported impulsivity scores and inhibition deficits, showing that heroin-addicted individuals do not have insight of their actual mental or physical condition. Moreover, a recent study suggested that heroin users' insight seems to improve with severity and progression of their addiction,implying that early-phase addiction is characterized by a stronger deficit in awareness of the illness(Maremmani et al., 2012). Patients withinsight were characterized by a higher education level, expanded mental deficits due to prolonged heroin use, unsuccessful short-term treatment enrollments, as well as depression comorbidity(Maremmani et al., 2012).When Verdejo-García and Pérez-García (2008)asked polysubstance abusers (PSA) and their informants to assess their behavior through the FrSBe task, they found enhanced behavioral symptoms of PSA and significant discepancies in FrSBe scores between addicted individuals and their informants. On the other hand, no diminished insight into PSA's condition, as well as no significant differences in responses of both PSA and informants were reported during the abstinence period(Verdejo-García and Pérez-García, 2008).

Emotion recognition is essential to social readjustment and interaction(Blair, 2003; Fernández-Serrano et al., 2010). However, neural substrates that are responsible for emotion recognition are also involved in drug addiction(Verdejo-García and Bechara, 2009)and thus they were found to be impaired(Rosselli and Ardila, 1996; Reay et al., 2006; Homer et al., 2008).To the best of our knoweledge, the relationship between heroin addiction and emotion recognition has not been studied, but a lot of work has been conducted on other illicit drugs such as alcohol(Frigerio et al., 2002), polysubstance abuse(Foisy et al., 2005; Fernández-Serrano et al., 2010), opiates(Kornreich et al., 2003), cocaine(Kemmis et al., 2007) and psychostimulants(Verdejo-García et al.,

2007a). The most consistent finding was the abnormal recognition of negative emotions that is independent of abstinence length(Fernández-Serrano et al., 2010).Abstinent PSA showed poorer facial recognition of anger, fear and disgust and sadness, despite the length of abstinence but no significant difference was found in recognition of neutral or positive emotions, including surprise and happiness, relative to the control group(Fernández-Serrano et al., 2010). The duration of cocaine use was positively correlated to poorer processing of fear and anger, whereas the severity of cocaine use could predict weaker anger recognition(Fernández-Serrano et al., 2010). On the contrary, Woicik et al. (2009) reported no abnormal emotional processing in cocaine abusers, compared to the healthy group. Furthermore, alcoholics performed poorly in emotion recognition compared to opiate users under a methadone-maintenance program(Kornreich et al., 2003). In addition, the study of Leppänen (2006) revealed that depressed individuals had an increased sensitivity to recognition of negative emotions. Therefore, substance individuals that are comorbid to other mood disorders such as depression, alexythymia or irretability might present a better performance in negative emotions' recognition (Fernández-Serrano et al., 2010).

The Role of Different Brain Regions involved in Heroin Addiction

The prefrontal cortex (PFC) is the most affected brain region in heroin addiction. It is involved both in inhibitory control and in decision making and its dysfunctions result in satisfaction of immediate rewards and consequently in relapse(Zhang et al., 2011). The PFC also restrains craving(Ma et al., 2010) and is impaired in heroin addiction. The PFC is responsible for instrumental learning(Zhang et al., 2011), self-monitoring (Wang et al., 2012), orientation of actions, goals' representation and determination of stimulus' valence(Liu et al., 2009a). Impairments of dopamine's modulation in the PFC might be related to compulsive drug-taking behavior(Volkow and Fowler, 2000). Furthermore, abnormal cortical thickness in the PFC has been also reported in heroin addiction and may result in self-control loss, heroin's habituation and compulsiveness (Li et al., 2013a). Hypoperfusion in the PFC has been associated with impairment of metabolism, neural and glial function as well as GM volume's reduction(Denier et al., 2013a) and euphoria (Blum et al., 2013). In addition, hypoperfusion of the frontal lobe has been found during withdrawal condition (Rose et al., 1996) whereas enhanced blood oxygenation level-dependent (BOLD) has been reported during craving (Zijlstra et al., 2009). Furthermore, dysfunctions in the PFC have been directly involved in impulsive behavior that characterizes heroin-dependent individuals(Denier et al., 2013b; Qiu et al., 2013). Cognitive impairments have been further seen as GM deficits in frontal lobe(Wang et al., 2012) whereas prefrontal GM volumeatrophy and frontal WM deficits might be a biomarker for behavioral and neuropsychological deregulations underlying heroin addiction(Lyoo et al., 2006; Li et al., 2013c; Zhang et al., 2013). However, the reversibility in GM alterations might provide an explanation for the recovery of several cognitive skills andanxiety(Wang et al., 2012). Furthermore, abnormalities in two basic anatomical regions of the PFC such as the medial PFC (MPFC) and the dorsolateral PFC (DLPFC) have been reported in numerous studies.

The MPFC has been implicated in stress and reward processing(Zhang et al., 2011), thus heroin-induced GM volume deficits might be associated with the impulsivity of heroin-addicts. Furthermore, during the self-referential processing it treats the temporal information flexibly(Denier et al., 2013a). Moreover, a diminished perfusion in the MPFC of addicted individuals has been involved in emotional and self- disruption(Denier et al., 2013a). Reduced rsFC strength found in the MPFC and amygdale has also been linked to emotional dysregulation(Wang et al., 2010; Sutherland et al., 2012). On the other hand, the dorsolateral part of PFC is centrally associated with decision-

making(Krawczyk, 2002; Yuan et al., 2010b) and high-order cognitive tasks such as self-control, planning, working memory and attention focusing(Garavan et al., 2000; Wang et al., 2013), that are all compromised in heroin addiction. The reduced GM intensity located in the DLPFC has been implicated in goal-oriented behavior dysfunctions and erroneous decisions(Yuan et al., 2010b). Dysfunctions in DLPFC have been further linked to heroin-conditioning(Moreno-López et al., 2012) that is carried out retrieving memories biased towards heroin-related stimuli, maintaining and orientating representations inherited from other brain regions during craving as well as choosing direct rewarding responses(Jiang et al., 2011; Wang et al., 2013).

The higher degree found in the DLPFC of the heroin-dependent group indicates that information transfer becomes more complicated in the addicted brain compared to the healthy one(Yuan et al., 2010c). Similar findings have been reported for the dorsal superior frontal gyrus that is a part of the DLPFC providing evidence for the poor-monitoring in heroin-addicts' daily life(Liu et al., 2009b). Moreover, the decreased functional connectivity between the DLPFC and the rostral part of the ACC might be interpreted as a functional dysregulation in response inhibition(Yuan et al., 2010a). In addition, GM density decrease has been detected in this brain region, probably leading to a functional disorganization of the brain, despite the fact that the exact causal relationship between functional connectivity and GM density deficits is still obscure(Yuan et al., 2010b). Moreover, the heroin-induced cognitive impairment and especially the degree its deficit was correlated with the activation's changes in prefrontal-cingulate network (Lee et al., 2005; Xiao et al., 2006; Galynker et al., 2007).

The cingulate gyrus constitutes another brain region severely affected in heroin addiction. It consists ofthe anterior cingulate gyrus (ACC) and the posterior cingulate gyrus (PCC)/precuneus (pC). The ACC is additionally subdivided into the ventral (vACC), the rostral (rACC) and the dorsal (dACC) part. The ventral part of ACC is the ACC's emotional component that is responsible for the stimulus salience and for the modulation of emotional responses(Ma et al., 2010). The vACC exhibits reduced functional connectivity with many different brain regions involved in heroin addiction, such as the nucleus accumbens (NAc), amygdala/ parahippocampal gyrus, thalamus and posterior cingulate cortex/precuneus(Wang et al., 2010). Hence, its dysfunctions seem to cause drug cue bias, encoding of reward expectancy, decision-making deficits and meditation of heroin-related stimulus salience(Peoples, 2002; Wang et al., 2010). The rostral part of ACC handles inhibition control(Liu et al., 2009b; Yuan et al., 2010a; Zhang et al., 2011). Therefore, its decreased functional connectivity with the OFC, DLPFC and the right middle temporal lobe of heroin-dependent individuals justifies the impairments in inhibition and decision control(Yuan et al., 2010a). Furthermore, an enhanced degree has been detected in the rACC of heroin-dependent individuals highlighting the complexity of information transfer(Yuan et al., 2010c).

The dorsal ACC constitutes the ACC's cognitive component that is involved both in conflict and error monitoring, as well as in inhibition control(Bush et al., 2000; Ma et al., 2010, 2011). Heroin-dependent subjects showed reduced functional connectivity between the dACC and the other DMN's components. This finding may explain the weakening of attentional coordination and self-monitoring(Ma et al., 2011). Reduced functional connectivity has been also reported between the dACC and the superior frontal gyrus(Wang et al., 2013). On the other hand, the increased rsFC between the right dACC and the lingual gyrus as well as the inferior parietal gyrusconfirm the role of dACC in selective attention and voluntary action(Weissman et al., 2002) in favor of drug-related cues (Cox et al., 2006). However, the reduced rsFC of dACC with several major components of social brain (middle temporal

gyrus, DLPFC, MPFC, PCC and temporal polar) justifies the disability of heroin-dependent individuals in social interactions(Wang et al., 2013).

The middle cingulate gyrus has been associated with emotional disgust and nausea indicating the reason of ignoring the unclear environment during the intoxication(Harrison et al., 2010; Li et al., 2013c). The PCC is a key area that is linked to reward prediction and visual orientation(Li et al., 2013b). Chronic exposure to heroin alters the intrinsic activities of PCC increasing the strength between the PCC and dorsal striatum and thus exposing the subject to risky and uncertain rewards or craving (Li et al., 2013b). Additionally, the PCC seems to be involved in episodic memory retrieval(Wagner et al., 2005). It also connects the anterior to the posterior part of the DMN. Nevertheless, the weakened rsFC found between the vACC and PCC might suggest the loss of synchrony between self-referential thoughts (vACC) and memory retrieval(Wang et al., 2010).

The orbitofrontal cortex (OFC) is the motivational/ drive core of the brain. Although, it has been shown to be hypoactive during withdrawal(Adinoff et al., 2001), exposure to drug-related stimuli seems to reinforce it(Zhang et al., 2011). Especially, during craving the OFC's activation is proportional to the intensity of craving(Volkow et al., 1991; Zhang et al., 2011). However, disruption in the functions of OFC could result in compulsive drug seeking or taking even when it is not activated(Rolls, 2000a). Enhanced activation of OFC could be experienced as a craving episode and alsochange the striatal activity(Zhang et al., 2011). The OFC is not a functionally homogeneous region since its medial part is involved in assessing the reward salience of reinforcers while its lateral aspect guides the behavior and evaluates the reinforcers' punishment value(Ma et al., 2010). The addicted brain is characterized by a disorganization of the OFC at rest that it is expressed by the functional abnormalities between NAc(Ma et al., 2010), vACC(Wang et al., 2010), rACC(Yuan et al., 2010a), amygdala(Xie et al., 2011) and OFC, the enhanced degree(Liu et al., 2009b; Yuan et al., 2010c), the regional heterogeneity(Qiu et al., 2011) as well as the diminished amplitude low-frequency oscillation(Jiang et al., 2011) in the aforestated brain region.

Memory/learning systems are also involved in heroin addiction because a place, an event, a person, or a heroin-related cue can retrieve memories and by extension trigger reward expectancy, craving and relapse(Zhang et al., 2011). The amygdala is responsible for the basic learning processes such as acquisition, unification and expression(Ma et al., 2010) and constitutes an essential hub of the impulsivity system(Xie et al., 2011). Therefore, learning of heroin-related stimuli might lead though signaling reward expectancy to craving and relapse(Ma et al., 2010). The existence of robust rsFC between the subcortical and temporal regions such as OFC(Ma et al., 2010; Xie et al., 2011), caudate, thalamus, insula, PCCand amygdala(Xie et al., 2011) and the abnormal topological properties(Liu et al., 2009b; Yuan et al., 2010c)located in the majority of the memory system's components explain the compulsive behavior of heroin-addicts. Moreover, the amygdala's interactions with other brain regions such as the MPFC, hippocampus, insula and cingulate gyrus reveal the amygdala's role as anemotional and stress regulating component(Pezawas et al., 2005; Stein et al., 2007; Sutherland et al., 2012).

The hippocampus partially mediates the declarative memory, which is the learning of emotional states related to heroin experience(White, 1996; Zhang et al., 2011). Declarative memory is a crucial function for the development of addictive behavior because it automatically stores information about heroin taking(Zhang et al., 2011). The enhanced activation of the hippocampus within the DMN that has been found in heroin-dependent individuals might underlie the increased sensitivity for heroin-related cues because the abnormal augmentation

of memory processing seem to mislead the subject's attention and the self-monitoring(Ma et al., 2011). The altered resting-state brain organization which is characterized by an increased degree was evident in theparahippocampal gyrus(Yuan et al., 2010c) as well as the hippocampus (Liu et al., 2009b).

Among the memory systems involved in heroin addiction are the putamen and the caudate. These brain regions have been associated with habit learning through which well-learned memories are stored and elicited by the relevant stimuli(Zhang et al., 2011). The caudate and putamen in conjunction with the pallidum, have been further linked to emotional and stress regulation because the dopamine release in the ventral striatum is enhanced under stressful conditions(Pruessner et al., 2004). Disruption of the resting-state striatum equilibrium in heroin-addicts might result in unexpected activation and subsequently in erroneous decisions and relapse(Liu et al., 2009b). Abnormal topological brain organization has been reported in the putamen and caudate(Yuan et al., 2010c). Furthermore, a diminished rsFC has been reported in the left caudate within DMN(Ma et al., 2011). A recent study(Kelly et al., 2009)showed that the caudate is presumably associated with the DMN's suppression during tasks with cognitive demand, thus caudate's dysfunction may underlie the disability of DMN's suppression.

The nucleus accumbens (NAc) plays a crucial role in reward processing. It has been linked to reward salience evaluation and motivation and is highly affected in heroin addiction(Wang et al., 2010; Zhang et al., 2011). The NAcinteracts and is strongly connected with the ventral tegmental area (VTA), OFC, ACC and hypothalamus(Robinson and Berridge, 1993; Wang et al., 2010). The decreased rsFC between the vACC and NAc provides evidence for the hypersensitivity of heroin-dependent individuals towards reward responses(Wang et al., 2010). Furthermore, a linkage between the Nac's activity alterations and drug-related-stimuli induced craving has been confirmed (Kilts et al., 2004; Myrick et al., 2004) despite the neurochemistry of stimuli-induced craving is not understood (Childress et al., 2002).

The thalamus and insula are also implicated in heroin addiction, playing various roles. The thalamus is a midline brain region that succours the arousal, perception and attention(Wang et al., 2010). Dysfunction of the thalamus has been reported in heroin-addicts during an uninterrupted visuospatial attention task(Tomasi et al., 2007; Wang et al., 2010). However, its diminished resting functional connectivity with the vACC can be associated withattention and working memory dysfunctions(Wang et al., 2010). In line with this, regional heterogeneity, located in the medial dorsal nucleus of the thalamus justifies and explains the deficiency in organization, planning, attention, multitasking, abstract thinking and memory that are common characteristics of chronic heroin users(Qiu et al., 2011). In addition, there is increasing evidencefrom neuroimaging studies that both the thalamus and insula constitute components of an impulsivity-related network (Xie et al., 2011). Furthermore, opiate addicted individuals show a decreased FA value in thalamic radiation due to an increase of radial diffusivity indicating the existence of myelin pathology(Bora et al., 2010). Additionally, topological small-world distortion has been further detected in the thalamus and insula of heroin-dependent individuals(Liu et al., 2009b; Yuan et al., 2010c).

The insula serves multiple functions including emotional regulation, integrating information and compiling somatosensory information because it interacts with the thalamus, amygdala, OFC and striatum(Liu et al., 2009b). More precisely, it receives "homeostatic afferent" through the thalamus and sends its outcomes to brain

regions such as the striatum, amygdala and OFC(Liu et al., 2009b). Moreover, insula interacts with the frontal cortex constituting a frontal-limbic network that mediates both the control and the pleasure's appreciation (Mesulam, 2000; Clark et al., 2008; Li et al., 2013a). Therefore, disruption in the insulaencountered in chronic heroin abusers might be related to compulsive and impulsive drug-taking behavior(Liu et al., 2009b). Heroin-dependent subjects have shown diminished perfusion(Denier et al., 2013a) and decreased cortical thickness(Li et al., 2013a) in the insula which are indicative of emotional deregulation. Moreover, GM deficits seem to be responsible for impairments in self-inducedor internal emotional processing and also might result in the hypersensitivity to drug-related stimuli (Yuan et al., 2009).

Recent neuroimaging studies have provided important evidence on the role of cerebellum in heroin addiction. The cerebellum is implicated in conditioned emotional memory, decision-making and inhibition control and provides many receptors that can be exploitable by addictive substances such as heroin(Wang et al., 2013). Heroin impairments in the cerebellum has been revealed by the decreased rsFC between the cerebellum and PCC, that is a DMN's core component and can be interpreted as a disruption in decision making(Yuan et al., 2010a). Abnormal small-worldness has also been detected in heroin addicts,indicating the degree's increment in different brain regions, including the cerebellum(Yuan et al., 2010c). The altered ALFF(Wang et al., 2013) in the aforementioned brain region seems to reflect the reorganization of thecerebellum's network. FA and axial diffusivity reduction together with increased radial diffusivity, in the cerebellum's anterior vermis might be linked to demyelinationor fiber reconstruction and axonal injury(Lin et al., 2012). Finally, GM deficits have been reported in this brain area, suggesting the dysfunction of cerebellum(Yuan et al., 2009).

Based on the addiction model proposed by Volkow et al.(2003), the aforementioned brain regions are organized in four brain circuits interacting each other. The reward circuit is represented by the NAc and the ventral pallidum; the motivation/drive circuit is located in the subcallosal cortex and the OFC; the memory/learning circuit is formed by the amygdala and the hippocampus; the control circuit is located in the anterior cingulate gyrus and the prefrontal cortex. The interaction among these four circuits is achieved through direct dopaminergic innervations as well as with other direct or indirect projections. However, other brain regions could be involved in the circuits such as caudate and putamen in memory/learning circuit. Moreover, brain regions such as the anterior cingulate cortex could take part in more than one circuits as well as other brain regions could be affected in drug addiction. Additionally, recent studies have revealed the implication of other circuits such as valuation networks (executive and reward networks), attentional and emotional networks.

Typically, when we exposed to a stimulus our response is affected by the expected reward which is partly processedby DA neurons projecting into the reward component NAc(Dehaene and Changeux, 2000). The hierarchy of stimuli's saliency value is modulated by both context and previous experience. Previous exposure to the stimuli makes its salience value to be affected by memory. Key components of memory are amygdala and hippocampus. Stored memories consist of associations between the stimulus and the affective state (positive or negative)which they experienced. The activation of DA facilitates the associations' establishment(Di Chiara, 1999). Subsequently, the salience value of the stimulus is weighted against other alternative reinforcers as a function of the momentary and internal need of the person. The shifting of the reinforces' relative value is partly processed by the OFC(Rolls, 2000b; Schultz, 2000). The final part is the cognitive decision to act or not to get the stimulus which is mediated by the cingulate gyrus and the prefrontal cortex(Miller and Cohen,

2001).Therefore, the stronger the reward expectancy of a stimulus stemming from previous exposure, the greater the motivation and the drive to procure it (see Figure 4).

In addicted subjects, the expected reward properties are enhanced leading to increased motivation and drive. The enhanced salience value of the drugs could be attributed to multiple reasons. Firstly, the drugs induce three- to fine-fold greater increases in DA in the NAc compared to natural reinforcers (e.g. food and sex) resulting in very high intrinsic reinforcing effects(Wise, 2002). Moreover, the much higher reward properties of the drugs reset the reward thresholds decreasing the sensitivity to natural reinforcers(Koob, 2001). Consequently, among no other competitors the drugs constitute the main motivational drive for the individual. The overactivation of motivational key-brain regions such as OFC which is involved in prediction of reward has been linked to compulsive intake(Insel, 1992). Additionally,multiple memory/learning systems contribute to the compulsive drug consumption. The conditional learning mediated in part by the amygdala and the NAc is responsible for the combination of neutral stimuli (e.g. a place) with the drug abuse as well as its reward and motivationalproperties. The habit learning partly mediated by the putamen and the caudate contributes to establish well-learned behavior sequences that are caused automatically by the exposure to appropriate stimuli. Moreover, the declarative memory controlled in part by hippocampus is responsible for the associations built between the stimuli and the positive or negative experience while procuring the stimuli. Finally, they used to take inadequate decisions in favor of immediate rewards instead of delayed but more favorable responses (see Figure 4). In line with this are both the disruption of PFC found in addicted individuals(Volkow et al., 2003) as well as the imbalanced link between the β- (reward network) and δ- (executive network) networks (Xie et al., 2014).

[Figure 4]

The correlation of heroin-induced impairments with the chronicity of use

Several neuroimaging studies have correlated functional connectivity alterations, structural deficits and abnormal topological properties with the duration of heroin use indicating its cumulative effect.

In a heroin-abstinent group, the duration of heroin use was positively correlated with the degree (D) in several brain regions such as the cerebellum bilaterally, left putamen and right parahippocampal gyrus. On the other hand, it was negatively correlated with the shortest path length in the same brain regions suggesting that a longer heroin use results in more complicated information transfer (Yuan et al., 2010c). Moreover, alterations in the rsFC of rACC and PCC were negatively correlated with the chronicity of heroin use(Yuan et al., 2010a). In line with this, the GM density deficits in the right DLPFC and its rsFC with the left inferior parietal lobe were also negatively associated with heroin's continuation(Yuan et al., 2010b). This means that is the longer heroin use, the more extended the GM density loss and the more weak rsFC between the right DLPFC and the left inferior parietal lobe resulting in cognitive control and decision-making impairments(Yuan et al., 2010b). Another structural characteristic such as gray matter volume in the prefrontal cortex exhibits an inverse relationship with heroin's effect(Qiu et al., 2013). According to Qiu et al. (2011)heroin addiction has a cumulative effect on the regional homogeneity of the lingual gyrus, cuneus bilaterally and medial OFC. The negative correlation of caudate's ALFF with the duration of heroin use might indicate that a diffusive neural and dopaminergic dysfunction as well as the strengthening of drug-seeking habit may occur after long-term heroin use(Wang et al., 2013). Furthermore, an altered strength between the PCC and insula, as well as between the

PCC and striatum might appear in the addicted brain after chronic heroin exposure(Li et al., 2013b). Long-term opiate dependence has been shown to affect the axonal diffusivity mainly in the frontal WM and superior longitudinal fascicule indicating an extended impact on neural function(Bora et al., 2010). GM density deficits in the prefrontal and temporal regions and ACC excluding cerebellum and insula are aggravated proportionally to long-term heroin addiction(Yuan et al., 2009).Widespread impairment in social and executive functioning, impulsive behavior and inhibition control are consistent traits of chronic heroin-dependent individuals which can be attributed to increasingly reduced FA values in the frontal sub-gyrus relative to chronic exposure to heroin(Liu et al., 2008). Dominant abnormalities in decision-making, comorbid mood states and self-control loss, might be attributed to the progressive reduction of cortical thickness observed in insular and superior frontal regions(Li et al., 2013a). Although several impairments in GM density seem to subside after a one-month abstinence, significant GM density loss still remains in the left cingulate and inferior occipital gyrus, as well as in the right middle frontal gyrus, providing evidence for the severe cumulative effect of heroin addiction(Wang et al., 2012). Therefore, an early intervention is of utmost importance in the treatment of heroin addiction.

Limitations of existing resting-state literature

The functional and structural exploration of the brain of heroin-dependent individuals has been possible with the help ofdifferent computational techniques (Liu et al., 2008, 2009a; Bora et al., 2010; Wang et al., 2010, 2011, 2012, 2013; Yuan et al., 2010a, 2010b; Ma et al., 2010, 2011; Qiu et al., 2011, 2013; Zhang et al., 2011, 2013; Moreno-López et al., 2012; Lin et al., 2012; Denier et al., 2013a, 2013b; Li et al., 2013a, 2013b). One reason for the controversial results reported by different studies could be the inadequacy and the heterogeneity of the participant samples. The majority of studies have based their results on less than thirty participants(Li et al., 2013b; Liu et al., 2009b; Ma et al., 2011, 2010; Yuan et al., 2010a, 2010b, 2010c; Zhang et al., 2011). Furthermore, in most studies participants were of both genders(Lyoo et al., 2006; Liu et al., 2008; Yuan et al., 2009; Wang et al., 2010; Jiang et al., 2011; Qiu et al., 2011, 2013; Lin et al., 2012; Moreno-López et al., 2012; Denier et al., 2013a, 2013b).

Moreover, the disregard of methadone and nicotine effects in some studies may haveinhibited the extraction of reliable results. The reported correlation betweenlong-term methadone maintenance treatment and WM's myelin atrophy indicates that findings on WM's impairments may be confounded by the direct or indirect effect of methadone(Lin et al., 2012). Although it has been shown that methadone is beneficial for the brain's chemistry and function(Kaufman et al., 1999; Gruber et al., 2006), it might cause dysfunctions in a wide range of cognitive tasks such as sustained attention, processing speed, endurance in distractibility and visuospatial perception. Thesedysfunctions have been proven in subjects going through different abstinence phases(Rose et al., 1996; Mintzer and Stitzer, 2002; Mintzer et al., 2005; Prosser et al., 2009). Furthermore, the disruption of dopamine neurons in the striatum of former heroin-addicts under methadone maintenance treatment, has been shown(Shi et al., 2008). In addition, methadone has been implicated in inducing craving and heroin expectancy under relevant stimulation (Curran et al., 1999). A reinforcement of sensitivity to drug stimuli could be a result of methadone (Langleben et al., 2008). Although there is no direct assessment of methadone's effect, the accumulated effect of methadone has been linked to the intensity of WM integrity deficit in the right frontal lobe as well as in the cingulate gyrus' left splenium (Wang et al., 2011). Moreover, the increased ALFF in parietal lobe has been

positively correlated with the methadone's dose suggesting that could be a biomarker of methadone-maintenance program's success (Jiang et al., 2011).

The majority of existing resting-state studies have been conducted on smokers (Liu et al., 2008, 2009a; Wang et al., 2010, 2012; Ma et al., 2010, 2011; Qiu et al., 2011, 2013; Jiang et al., 2011; Moreno-López et al., 2012; Denier et al., 2013a, 2013b; Li et al., 2013a, 2013c), without taking into account the nicotine's effecton their findings.In an earlier study, nicotine was linked to reduced GM density in the PFC bilaterally and the right cerebellum(Brody et al., 2004), brain regions that are vulnerable to heroin addiction. Furthermore, it has been shown that nicotine reduces the possibility of developing Parkinson's disease by a neuroprotection mechanism(Quik, 2004). Last but not least, smoking has been associated with thedisruption in the insula(Naqvi et al., 2007) which is a consistent finding in heroin addiction(Lyoo et al., 2006; Liu et al., 2009b; Wang et al., 2010; Xie et al., 2011; Denier et al., 2013a; Li et al., 2013a, 2013b).

According to Rapeli et al. (2006), the drugs' effect is related to the length of the abstinence period, indicating that the duration of abstinence could influence alterations in an individual's cognitive performance. Many studies have been performed on users being short-term abstinent (Lee and Pau, 2002; Mintzer et al., 2005; Fishbein et al., 2007; Verdejo-García et al., 2007b; Wang et al., 2010; Jiang et al., 2011, 2013; Li et al., 2013b, 2013c)whereas in others active drug users were recruited (Liu et al., 2008, 2009a; Qiu et al., 2013; Wang et al., 2013; Zhang et al., 2013). Moreover, other researchers have studied either mixed cohorts(Bora et al., 2010), including participants in different abstinence phases(Ma et al., 2010, 2011) or prolonged-abstinent individuals (Liu et al., 2009b; Wang et al., 2011; Lin et al., 2012; Moreno-López et al., 2012; Zeng et al., 2013). Finally, in other studies, the duration of abstinence is not clearly stated(Lyoo et al., 2006; Qiu et al., 2011).Consequently, the difference in abstinence length might justify the inconsistent findings across the existing studies and more research is needed to handle this issue.

Furthermore, methadone in the initial phase of methadone replacement therapy has been shown to be slowly-metabolized(Corkery et al., 2004). More specifically, according to Wolff et al. (2000) the median elimination half-life of methadone has been found to be diminished more than 60% when the addict has reached a steady-state methadone level. Thus, patients suffering from addiction who are methadone-naïve are in a high risk of overdosing specifically during the initial phase of methadone maintenance treatment programs(Drummer et al., 1992; Caplehorn and Drummer, 1999; Milroy, 2000; Wolff et al., 2000; Corkery et al., 2004).

Future Outlook

Given the widespread and multilevel damage that can be caused by drug addiction, it is crucial to design and develop appropriate therapeutic interventions in order to both rehabilitate and improve the abilities of heroin-addicted individuals. The existing pharmacological, behavioral and psychosocial interventions have been criticized as being of limited use(Fagan, 1994; Dehghani-Arani et al., 2013). Despite the improvement achieved by various pharmacological interventions, both the side effects and the high risk of relapse must be considered when pharmacotherapy is used as a unique treatment approach(Fagan, 1994; Gossop et al., 2002). Moreover, there are medications that are not covered by insurance plans(McGovern et al., 2013). Even if clinicians are trained to perform psychosocial treatments, such as a cognitive behavioral treatment, they cannot prevent the relapse due to the lack of unremitting patients' supervision (McGovern et al., 2013). Furthermore, the relapse

rate of the existing treatment practices has been reported to be over 70%(Higgins et al., 1995). Last but not least, the treatment outcomes were found to be short-term because 60% of the patients relapsed one year after treatment completion(Gossop et al., 2002).

A novel treatment approach is cognitive enhancement through video games,which has been shown to be promising in the treatment of early-phase schizophrenia and autism(Sahakian et al., 2010; Insel et al., 2013). Additionally, the fact that abstinent heroin individuals performed as well as healthy subjects, with appropriate motivation, in IGT-like tasks(Zeng et al., 2013) as well as the fact that gambling card games are very popular among drug-users in China(Xu, 2012), games could be an efficient tool in order to alleviate compulsive drug-seeking behavior and to enhance social behavior.

Neurofeedback is a brainwave biofeedback technique(Hammond, 2011) based onoperant conditioning that might be a promising treatment tool to regulate brain plasticity in a natural, non-invasive and painless way(Ros et al., 2010) but it is not widely accepted due to its limited use (Dehghani-Arani et al., 2013). Demos (2005) defined neurofeedback as a therapeutic method that is designed for mind and body optimal training resulting in cognitive, physical, emotional and behavioral improvement. In practice, it is used to inhibit or reinforce specific EEG rhythms (Scott et al., 2005) assisting the deviating psychological states to turn into normal ones (Gunkelman and Johnstone, 2005). As Ros et al (2014) postulate, neurofeedback tunes brain waves toward homeostasis, thereby leading to optimal network stability while maintaining flexibility. It is known that brain plasticity is the ability of the brain to change functionally and structurally (Kolb and Whishaw, 1998). It is also known that experience induces alterations in dendritic length, spine density, glial and metabolic activity as well as it assists in synapse formation (Kolb and Whishaw, 1998). These structural changes lead to behavioral modulations and they seem to be affected by diverse factors including brain pathology, aging, stress, as well as, trophic and gonadal factors (Kolb and Whishaw, 1998). Moreover, it was revealed in a recent study that the control of natural human brain using brain-computer interface (BCI) results in sustained excitability of motor cortex indicating not only that brain oscillations could mediate plasticity (Ros et al., 2010), but also that BCI methods lead to functional modulations.

In that sense, neurofeedback is efficient because it can improve the neuropsychological and psychological state of the patient, debilitate the drug-induced compulsive behavior and lead to long-time abstinence(Peniston and Kulkosky, 1989; Masterpasqua and Healey, 2003; Scott et al., 2005; Sokhadze et al., 2008; Dehghani-Arani et al., 2013). It has already been used as a therapeutic method in various mental illnesses, such as depression(Putman, 2002), attention-deficit/hyperactivity(Fuchs et al., 2003; Rossiter, 2004; Strehl et al., 2006; Kropotov et al., 2007), obsessive compulsive disorder(Hammond, 2003), epilepsy(Kotchoubey et al., 2001), anxiety and affective disorders(Hammond, 2005). Moreover, some studies have confirmed its efficiency in weakening the neuropsychological traits of substance and alcohol dependence(Saxby and Peniston, 1995; Masterpasqua and Healey, 2003; Scott et al., 2005; Sokhadze et al., 2008). Gruzelier provides important aspects and recommendations to this direction by examining spheres of cognitive, affective and behavioralenhancement with neurofeedback (Gruzelier, 2014a) as well as a range of fascinating insights about underpinnings from multi-modal methodologies in addition to numerous methodological and theoretical issues (Gruzelier, 2014b; Gruzelier, 2014c; Gruzelier et al., 2014).

In conclusion, a major future goal for multimodal heroin addiction neuroscience research has to be the development of an integrated therapeutic model that would include classical treatment practices, enriched by current neurotechonologies, such as neurofeedback and goal-oriented video-games.Following the aforementioned combined treatment approach one could achieve both psychological state stability in the beginning of the treatment, using pharmacotherapy, behavioral and psychosocial approaches, but also long-lasting outcomes and minimal side effects, with the help of neurofeedback and video-games.

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Appendix A

Resting-State Functional Connectivity Alterations in Heroin-Dependent Individuals			
Study (year)	Sample	Method	Results
Ma et al. (2010)	HD: 14 (M/F: 14/0) (30.1±5.3 years) Heroin use: 7.11±2.82 years Detoxification phase: 9 entered the methadone-treatment program before 2.1±1.8 days, 2 were in 6 months program, 1 was in a 2 months program and 2 were active heroin users) Daily dose of methadone: All participants under daily methadone-treatment program received their last dose 12 hours before the experiment, but the daily dose of methadone was not stated. Nicotine use: Smoker participants but the daily nicotine dose was not stated. Education: 9.71±2.7 years CN: 13(M/F: 13/0) (29.8 ±7.2 years) Nicotine use: Smoker participants but daily nicotine dose was not stated. Education: 10.8±1.6 years	fMRI seed-based correlation analysis	HD>CN: Right NAc and left ventral/rostral ACC, left NAc and left vACC/ medial OFC, left medial OFC and right medial OFC, left lateral OFC and right medial OFC, right amygdala and left lateral OFC. HD<CN: Left NAc and left precuneus, left medial OFC and left IFG, right lateral OFC and left lateral OFC/IFG, bilateral dorsolateral PFC, medial and right anterior PFC and right IPL, left dACC and left ventral/rostral ACC and left dorsolateral PFC as well as left lateral OFC and bilateral dorsolateral PFC, left insula, left lateral OFC, left IFG and medial PFC.
Wang et al. (2010)	HD: 15 (M/F:13/2) (41.0 ± 5.6 years) Heroin use: 19.9±3.1 years Detoxification phase: Active heroin users with last heroin use 3-7 hours (5.1±0.29 hours) prior to testing. Nicotine use: Smoker participants but the daily nicotine dose was not stated. Education: not stated CN: 15 (M/F:13/2) (38.4 ± 6.8 years) Nicotine use: Smoker participants but the daily nicotine dose was not stated. Education: not stated	fMRI ROI-seed based correlation analysis vACC ([6 39 -4] in Talairach space) selected as ROI	HD: Significant rsFC was reported between the vACC and the left inferior and middle temporal gyrus, the left transverse temporal gyrus as well as the insula, the ACC, the superior temporal gyrus and the OFC/MPFC all bilaterally. CN: Strong rsFC was found between the vACC and several brain regions such as left inferior and middle temporal gyrus, right superior temporal gyrus and PHG as well as the OFC/MPFC, NAc, PCC/pC and ACC bilaterally. HD>CN: vACC and bilateral middle temporal gyrus, left ventrolateral PFC and bilateral superior temporal gyrus. HD<CN: vACC and bilateral PCC/pC and ACC as well as NAc, PHG/Amygdala and thalamus in the right hemisphere.

K. Yuan et al. (2010)	HD: 11 (M/F:11/0) (37.2±7.3 years) Heroin use: 89.5±55.7 months Dose of heroin use: 0.6±0.3 g/day Detoxification phase: Abstinent heroin-dependent subjects with mean abstinence length 4.9±0.8 months. Dose of methadone on the experiment's day: 34.2±18.7 mg. Nicotine use: not stated Education: 9.8±2.5 years	fMRI Discrete Cosine Transform (DCT) analysis	HD: Strong rsFC was found between the PCC/Precuneus and the right DLPFC and bilateral angular gyrus and middle temporal lobe. Furthermore, significant rsFC was found between the rACC and the left middle temporal lobe as well as the bilateral OFC and thalamus. CN: Significant rsFC was showed between the PCC/Precuneus and DLPFC, parahippocampal and angular gyrus, middle temporal lobe as well as MPFC including OFC and ACC, all bilaterally. Moreover, strong rsFC was reported between the rACC and the left PCC and the hippocampus, the OFC and the middle temporal lobe all bilaterally.
	CN: 13 (M/F:13/0) (36.8 ± 7.4 years) Nicotine use: not stated Education: 9.1±3.2 years		HD<CN: PCC/Precuneus and the right cerebellum as well as the left DLPFC, rACC and right middle temporal lobe and both OFC and DLPFC in the left cerebrum.
G. Jiang et al. (2011)	HD: 24 (M/F: 20/4) (35.67±5.662 years) Heroin use: 10.83±4.613 years Dose of heroin use: 0.6±0.4 g/day Detoxification phase: They were hospitalized for about a week (6-7 days) prior to the scanning. Dose of methadone on the experiment's day: 35.38±10.38 g/day Nicotine use: 19.38±9.245 (no.cigarettes/day) Education: 10.79±2.670 years CN: 24 (M/F: 20/4) (35.38±6.020 years) Nicotine use: 16.25±9.237 (no.cigarettes/day) Education: 11.21±3.527 years	fMRI Amplitude Low-Frequency Fluctuation (ALFF) analysis	HD>CN: Increased ALFF was detected in the post cingulate cortex/precuneus, the supramarginal and angular gyrus all bilaterally and also in the left middle frontal gyrus.
			HD<CN: Decreased ALFF was found in the DLPFC, the middle and inferior temporal gyrus as well as in the cuneus and the posterior cingulate cortex in the left hemisphere. Moreover, in the dACC and the medial OFC bilaterally.
C. Xie et al. (2011)	HD: 30 (M/F: 30/0) (33.05±6.04 years), 8 HU were excluded because of motion artifacts. Heroin use: 6.59±3.72 years Dose of heroin use: 0.96±1.26 g/day Detoxification phase: Abstinent heroin-dependent subjects with mean abstinence length 8.05±2.51 weeks Dose of methadone on the experiment's day: not stated Nicotine use: not stated	fMRI Intrinsic amygdala functional connectivity network (iAFC network)	HD: Significant positive correlation with amygdala was found in the middle and superior temporal gyrus, also in the posterior cingulate cortex, FFA, lingual gyrus, insula, thalamus, caudate, lentiform nucleus and OFC all bilaterally. Strong negative correlation with amygdala was detected in the parietal, occipital and prefrontal system including bilateral DLPFC, IFG, MeFG and IPC. CN: Significant positive correlation with iAFC network was showed in bilateral middle temporal gyrus and amygdala as

			well as in the ACC, superior temporal gyrus and OFC in the right cerebrum. Strong anticorrelations with iAFC network was found in the right FFA, left cerebellum and lingual gyrus and moreover in the bilateral IPC, DLPFC, IFG, MeFG and precuneus.
	Education: 10.86±2.40 years CN: 20(M/F: 20/0) (28.91±7.82 years), 5 CN were excluded because of motion artifacts. Nicotine use: not stated Education: 9.83±2.94 years		HD-CN: Alteration of iAFC's network correlations between two groups was mentioned. Increased positive correlation with iAFC network was detected in the right insula and in the thalamus bilaterally. However, enhanced anticorrelation with iAFC network was found in the right IFG whereas reduced anticorrelation was detected in left precuneus. Furthermore, the correlation with iAFC network in the right precuneus altered from positive to negative.
Zhang et al. (2011)	HD: 12 (M/F: 12/0) (37.2±7.3years) Heroin use: 89.5±55.7 months Dose of heroin use: 0.6±0.3g/day Detoxification phase: Abstinent heroin-dependent subjects with mean abstinence length 4.9±0.8 months Dose of methadone on the experiment's day: 34.2±18.7 mg Nicotine use: not stated Education: 9.8±2.5 years CN: 13 (M/F: 13/0) (36.8±7.4years) Nicotine use: not stated Education: 9.1±3.2 years	fMRI Pattern classification technique	HD-CN: High accuracies were reported in the amygdala, putamen, caudate, thalamus, posterior insula, OFC, ACC and the hippocampal/parahippocampal brain regions as well as in the CG.
Ma et al. (2011)	HD: 14 (M/F: 14/0) (30.1±5.3 years) Heroin use: 7.11±2.82 years Detoxification phase: 9 entered the methadone-treatment program before 2.1±1.8 days, 2 were in 6 months program, 1 was in a 2 months program and 2 were active heroin users) Daily dose of methadone: All participants under daily methadone-treatment program received their last dose 12 hours before the experiment, but the daily dose of methadone was not stated. Nicotine use: Smoker participants but the daily nicotine dose was not stated. Education: 9.71±2.7 years	fMRI Independent Component Analysis (ICA)	HD>CN: Increased rsFC was detected in right hippocampus within the DMN.
			HD<CN: Reduced rsFC within DMN was reported both in the right dACC and in the left caudate.

	CN: 13(M/F: 13/0) (29.8 ±7.2 years) Nicotine use: Smoker participants but the daily nicotine dose was not stated. Education: 10.8±1.6 years		
Li et al. (2013)	HD: 14 (M/F: 14/0) (35.4±6.4 years) Heroin use: 89.3±50.5 months Dose of heroin use: 0.6±0.4 g/day Detoxification phase: Abstinent heroin-dependent subjects with mean abstinence length 17.6±5.7 days Daily dose of methadone: not stated FTND: 5.83±2.6 Education: 9.4±2.6 years CN: 15 (M/F: 15/0) (31.9±6.8 years) FTND: 5.39±2.7 Education: 9.2±2.4 years	fMRI ROI-seed based correlation analysis PCC ([-4 -45 24] in Talairach space) selected as ROI	HD>CN: Greater rsFC was found between the PCC and the dorsal striatum and the insula bilaterally, the right supramarginal gyrus as well as the right IPL.
Wang et al. (2013)	HD: 17 (M/F: 17/0) (33.9±6.3 years) Heroin use: 81.5±33.9 months Dose of heroin use: 0.71±0.35 g/day Detoxification phase: Active heroin users. Nicotine use: 20.0±6.1 (no.cigarettes /day) Education: 10.2±2.8 years CN: 15 (M/F: 15/0) (34.3±7.3 years) Nicotine use: 18.3±2.1 (no.cigarettes /day) Education: 10.6±2.4 years	fMRI Amplitude Low-Frequency Fluctuation (ALFF) analysis and seed-based correlation analysis	HD>CN: Increased ALFF was reported in left superior occipital and temporal gyrus as well as in the cerebellum bilaterally. Increased rsFC was mentioned between the caudate and the cerebellum in the right hemisphere. HD: Enhanced rsFC was observed between the right dACC and the right IPL and lingual gyrus as well as the bilateral inferior frontal gyrus. Significant rsFC between the right dACC and the left superior frontal, temporal and posterior frontal gyrus, the right medial frontal gyrus as well as the middle temporal gyrus bilaterally was reported.
			HD<CN: Reduced ALFF was found in caudate, superior medial frontal cortex (DLPFC) and dACC in the right hemisphere. Decreased rsFC was showed between the right caudate and the right superior frontal and temporal gyrus, the left angular gyrus and the middle frontal gyrus bilaterally.

Abnormal Resting-State Topological Properties in Heroin-Dependent Individuals

J. Liu et al. (2009)	HD: 12 (M/F: 12/0) (41±5.6 years) Heroin use: 16.0±3.5 years Dose of heroin use: 1.0±0.7 g/day Detoxification phase: Abstinent heroin-dependent subjects with mean abstinence length 6.0±10.6 months Nicotine use: Smoker participants but the daily nicotine dose was not stated. Education: 8.2±1.8 years CN: 12 (M/F:12/0) (35.4±7.1 years) Nicotine use: Smoker participants but the daily nicotine dose was not stated. Education: 9.1±2.8 years	fMRI Graph Theory Analysis	HD>CN: Strong connectivity was detected in SMA, amygdala, hippocampus, ACC, putamen, caudate, pallidum, dorsolateral superior frontal and inferior orbitofrontal gyrus and insula. The degree between inferior orbitofrontal and dorsolateral superior frontal gyrus was increased in heroin-dependent group relative to controls.
			HD<CN: The small-worldness scalar was found significantly reduced.
K. Yuan et al. (2010)	HD: 11 (M/F:11/0) (37.2±7.3 years) Heroin use: 89.5±55.7 months Dose of heroin use: 0.6±0.3 g/day Detoxification phase: Abstinent heroin-dependent subjects with mean abstinence length 4.9±0.8 months. Dose of methadone on the experiment's day: 34.2±18.7 mg. Nicotine use: not stated Education: 9.8±2.5 years CN: 11 (M/F:11/0) (36.8 ± 7.4 years) Nicotine use: not stated Education: 9.1±3.2 years	fMRI Graph Theory Analysis	HD>CN: Higher degree was detected in many brain regions such as OFC, precuneus, rACC, cerebellum, putamen, parahippocampal gyrus and DLPFC, all bilaterally; thalamus, PCC, caudate, inferior and medial prefrontal cortex in the left hemisphere and right middle aspect of temporal gyrus.
			HD<CN: The small-worldness scalar was found significantly reduced.
Liu et al. (2011)	HD: 16 (M/F: 16/0) (36.7±7.1 years) Heroin use: 85.3±46.2 months Dose of heroin use: 0.6±0.3g/day Detoxification phase: Abstinent heroin-dependent subjects with mean abstinence length 4.7±0.7 months. Average daily dose of methadone: 34.6±18.1 mg/day Nicotine use: not stated Education: 8.4±1.6 years CN: 16 (M/F:16 /0) (37.3±6.9 years) Nicotine use: not stated Education: 8.7±2.1 years	fMRI Graph Theory Analysis	HD>CN: Ten connections found to be stronger including striatum and ACC, striatum and PFC, parahippocampal and PCC, parahippocampal and PFC as well as within PFC.
			HD<CN: Sixteen connections showed reduced intensity including ACC and insula, thalamus and PFC, hippocampus/parahippocampal and striatum as well as within striatum.
			HD-CN: The small-worldness scalar was found to be significantly different between the groups. Functional dysregulation based on the degree difference was reported in various brain regions such as insula, thalamus, caudate, hippocampus, parahippocampal, amygdala, putamen, pallidus, PFC, PCC, ACC, anterior/posterior aspect of

			cerebellum as well as temporal cortices. More precisely, the MeFG found to be highly connected at rest whereas the ACC was significantly lower in heroin-dependent individuals relative to healthy participants.
Jiang et al. (2013)	HD: 17 (M/F: 15/2) (36.29±6.86 years) Heroin use: 9.21±5.28 years Dose of heroin use: 0.80 ±0.54 g/day Detoxification phase: They were hospitalized for about a week (6-7 days) prior to the scanning. Daily dose of methadone 39.41±20.45 g/day Nicotine use: 0-40(no.cigarettes/day) Education: 10.24±3.21 years CN: 15 (M/F: 12/3) (31.27±8.10 years) Nicotine use: 0-40(no.cigarettes/day) Education: 11.07±4.11 years	fMRI Graph Theory Analysis	HD: Three hubs were showed to be heroin-specific that are left postcentral gyrus and precuneus as well as middle frontal gyrus in the right cerebrum.
			CN: Three hubs were showed to be specific to controls including right precuneus, left middle frontal gyrus and right temporal pole.
			HD>CN: The global parameters characteristic path length and normalized characteristic path length were enhanced. Nodal metrics (degree and efficiency) observed to be augmented left in inferior occipital and lingual gyrus as well as in hippocampus.
			HD<CN: The global parameters clustering coefficient, global and local efficiency as well as small-worldness and normalized clustering coefficient were found to be reduced. Nodal metrics (degree and efficiency) observed to be declined in six regions (left middle frontal and inferior temporal gyrus, right thalamus and precuneus and middle dorsal aspect of cingulate gyrus bilaterally). Moreover, a subnetwork with nineteen brain regions loosely connected was detected in heroin-dependent group.

Structural Resting-State Deficits in Heroin-Dependent Individuals

Gray Matter

Lyoo et al. (2006)	OD: 63 (M/F: 32/31) (38.4±9.4 years) Opiate use: 16.8±9.5 years Detoxification phase: They were on methadone replacement therapy or methadone replacement therapy combined to cognitive behavioral therapy Dose of methadone on the scanning day: 67.3±26.8 g/day Nicotine use: allowed but not reported Education: 11.1±2.4 years CN: 46 (M/F: 25/21) (38.4±8.6 years) Nicotine use: allowed but not	MRI Voxel-based Morphometry	OD<CN: Reduced gray matter density in prefrontal and temporal brain regions. More precisely, the brain regions with diminished gray matter were right superior and inferior frontal cortex, left frontal, superior and middle frontal cortex as well as the medial frontal cortex bilaterally. Additionally, the same phenotype has been found in left fusiform cortex, right uncus, superior temporal cortex and insula bilaterally. No significant differences have been found in densities of both white matter and cerebrospinal fluid (CSF).

	reported Education: 15.2±3.1 years		
Yuan et al. (2009)	HD: 30 (M/F: 15/15) (25.0±2.4 years) Heroin use: 4.29±1.92 years Dose of heroin use: 0.5-1.2 g/day Detoxification phase: They received treatment for heroin abstinence for about 5 months prior to the scanning. The abstinence period was 4.93±1.04 months Nicotine use: 23.7 ±11.3 (no.cigarettes/day) Alcohol use: 1.07±2.33 (time/week) Education: 9.03±2.63 years CN: 34 (M/F: 19/15) (23.97±2.69 years) Nicotine use: not reported Education: 10.24 ±3.09 years	MRI Optimized Voxel-based Morphometry	HD<CN: Decreased density of gray matter has been found in anterior cingulate, prefrontal as well as temporal brain regions. Major regions of reduced gray matter density were insula (BA 13), ACC (BA 32), prefrontal regions (BA 45, 46, 25, 9, 11) and temporal cortex (BA 20). In most of the aforementioned brain regions where group differences have been detected, negative correlation was found between gray matter density and duration of heroin consumption apart from cerebellum and insula. However, non-significant effect was found between gray matter density and abstinence period length.
Liu et al. (2009a)	HD: 15 (M/F: 10/5) (30.47±6.17 years) Heroin use: 74.53±55.53 months Dose of heroin use: 1.26±1.09 g/day Detoxification phase: They received methadone maintenance treatment for 3.60±1.35 days before scanning. The highest methadone dose was 25.40±5.70 mg and the last methadone dose on the scanning day was 12.93±4.13 mg. Nicotine use: 21.33 ±5.16 (no.cigarettes/day) Education: 10.13±1.96 years CN: 15 (M/F: 10/5) (30.53±6.70 years) Nicotine use: non-smokers Education: 11.73 ±2.49 years	Structural MRI Optimized Voxel-based Morphometry	HD<CN: Decreased gray matter volume has been detected in three clusters: BA 6 of the left SMC, the BA9 of the right prefrontal cortex as well as the bilateral BA 24 of the CC. Non-significant results have been reported referring to the total incranial volume, volume of global white matter, cerebrospinal fluid and gray matter. Similar findings have been mentioned for the ratios WM/TIV, GM/TIV and CSF/TIV.

Yuan et al. (2010b)	HD: 11 (M/F: 11/0) (37.2±7.3 years) Heroin use: 89.5±55.7 months Daily dose of heroin use: 0.6±0.3 g/day Detoxification phase: They received methadone maintenance treatment with mean abstinence 4.9±0.8 months. The scanning was done at least 5-8 hours after methadone administration (34.2±18.7 mg). Nicotine use: 15.4±10.7 (no.cigarettes/day) Education: 9.8±2.5 years CN: 13 (M/F: 13/0) (36.8±7.4 years) Nicotine use: not reported Education: 9.1 ±3.2 years	MRI Voxel-based Morphometry	HD: IPL, insula, MCC and fusiform gyrus in the right cerebrum have been reported to have positive correlation with the right DLPFC. Moreover, reduced functional connectivity was detected between the right DLPFC and IPL bilaterally. Additionally, the connectivity between right DLPFC and the left IPL as well as the GM density of the right DLPFC have been negatively correlated to the chronicity of heroin use. CN: Several brain regions such as insula, caudate, putamen, OFC, IPL, ACC and MCC have been found to be positively correlated to the right DLPFC. HD<CN: Reduced gray matter density has been reported in the left IPL and middle cingulate cortex as well as in DLPFC and fusiform gyrus in the right hemisphere.
Wang et al. (2012)	HD: 15 (M/F: 15/0) (29.8±6.84 years) Heroin use: 4.35±3.51years Daily dose of heroin use: 1.23±0.55 g/day Detoxification phase: They had to be detoxified from all opioids during hospitalization which was confirmed by urine testing. Nicotine use: smokers but not reported the no.cigarretes/day Education: 8.85±0.88 years CN: 20 (M/F: 20/0) (30.2±7.10 years) Nicotine use: smokers but not reported the no.cigarretes/day Education: 9.30 ±0.92 years The experiment was performed at two time phases of abstinence: 3-days and one-month.	Structural MRI Voxel-based Morphometry	HD: Non-significant differences in gray matter density have been reported according to different abstinence period. HD<CN: Diminished gray matter density after 3-days abstinence have been located in left posterior cingulate regions, right superior frontal and middle frontal gyrus as well as the inferior occipital gyrus. However, after one-month abstinence similar pattern remained not only in the left cingulate and inferior occipital gyrus but also in the right middle frontal gyrus.
Qiu et al. (2013)	HD: 24 (M/F: 20/4) (35.67±5.662 years) Heroin use: 10.83±4.613 years Daily dose of heroin use: 0.6±0.4 g/day Detoxification phase: They were abstinent one-month before MRI scanning.	MRI Voxel-based Morphometry	HD: Negative correlations have been revealed between the duration of heroin use and the gray matter volume located in DLPFC and medial PFC bilaterally. HD<CN: Significant decreased gray matter volume has been observed in right fusiform cortex, DLPFC and medial PFC bilaterally. No significant group

	Impulsivity scores: 67.21±2.84 Nicotine use: 19.38±9.245 (no.cigarettes/day) Education: 10.79±2.670 years CN: 24 (M/F: 20/4) (35.38±6.020 years) Impulsivity scores: 63.33±3.761 Nicotine use: 16.25±9.237 (no.cigarettes/day) Education: 11.21 ±3.257 years All participants have completed the 30-item Barratt's Impulsiveness Scale (Chinese translation).		differences have been reported in the TIV, the total ratio GM/TIV and the volume of global GM. Negative correlation was found in all cohorts between impulsivity scores and gray matter volume in bilateral DLPFC and medial PFC.
White Matter			
Liu et al. (2007)	HD: 16 (M/F: 12/4) (30.19±6.67 years) Heroin use: 68.31±54.11 months Daily dose of heroin use: 1.12±1.00 g/day Detoxification phase: They were under methadone maintenance program for an average of 3.63±1.31 days before scanning. The highest methadone dosage received was 24.63±5.94 mg and the last methadone dose was 11.81±4.05 mg. Nicotine use: 21.25±5.00 (no.cigarettes/day) Education: 10.0±2.58 years CN: 16 (M/F: 12/4) (30.00±7.40 years) Nicotine use: non smokers Education: 11.69 ±3.32 years	Diffusion Tensor Imaging (DTI) Voxel-based Morphometry	HD<CN: White matter FA calculated through VBM analysis has been found reduced in the right frontal sub-gyrus and precentral gyrus as well as in the left middle cingulate gyrus. Additionally, FA analysis confirmed that white matter FA was diminished in the left cingulate and bilateral frontal brain regions. Also, negative correlation has been reported between FA values of right frontal sub-gyrus and the duration of heroin use.
Bora et al. (2010)	OD: 24 (M/F: 11/13) (29.8±6.9 years) Opiate use: 8.9±5.1 years Daily dose of opiate use: 0.93±0.71 g/day Detoxification phase: They were stabilized on substitution pharmacotherapy (methadone: 9; buprenorphine: 15) Nicotine use: not reported Education: 13.4±1.8 years Full scale IQ: 112.6±9.9 CN: 29 (M/F: 14/15) (31.5±8.1 years) Nicotine use: not reported	MRI Diffusion Tensor Imaging (DTI) Voxel-based Statistical using Tract-Based Spatial Statistic (TBSS)	OD<CN: White matter FA reductions have been located in CC, thalamus as well as in temporal, parietal, cerebellar and frontal tracts. More profound diminutions have been found in the CC extending to both ACC and parietal cortex and also in the left ILF and anterior thalamic radiation. The majority of FA decrements could be attributed to the increase of radial diffusivity. The left uncinated cluster has been the only exception where the FA reduction should be attributed to the axial diffusivity's decrease. A positive correlation has been revealed between the duration of opiate use and the

	Education: 15.0±2.3 years Full scale IQ: 113.0±10.9 The Wechsler Abbreviated Scale of Intelligence was used in order to assess the general intelligence of participants.		axial diffusivity in the right frontal and the SLF bilaterally.
Wang et al. (2011)	HD: 13 (M/F: 13/0) (37.0±7.1 years) Heroin use: 90.2±51.0 months Daily dose of heroin use: 0.6±0.3 g/day Detoxification phase: They were under methadone maintenance program for an average of 5.2±1.4 months before scanning. The methadone dosage received was 6.2±5.3 mg per day. Nicotine use: 18.0±18.7 (no.cigarettes/day) Education: 10.7±2.5 years PA: 11 (M/F: 11/0) (35.0±6.8 years) Heroin use: 89.1±59.6 months Daily dose of heroin use: 0.8±0.5 g/day Detoxification phase: They have undergone a detoxification phase of 6.5±1.0 months and they were receiving a drug-free treatment. Nicotine use: 18.7±1.4 (no.cigarettes/day) Education: 9.1±1.9 years CN: 15 (M/F: 15/0) (34.3±7.3 years) Nicotine use: 17.9±2.1 (no.cigarettes/day) Education: 10.6 ±2.4 years	MRI Diffusion Tensor Imaging (DTI)	PA-CN: No significant alterations in DTI measures have been reported. HD-CN: Higher ADC and radial diffusivity ($\lambda^{\perp}$) values have been found in left splenium and left genu of CC respectively. However, reduced FA value has been mentioned in the left genu of CC. HD-PA: Increased ADC value has been reported in the left genu of CC bilaterrally. HD: The acculated effect of methadone has been negatively correlated to the FA values in both left splenium of CC and right frontal lobe. Additionally, the axial diffusivity ($\lambda_{\parallel}$) tended to present a negative correlation with previous heroin consumption. PA: The accumulated heroin use was found to be negatively correlated with the ADC , the radial diffusivity ($\lambda^{\perp}$) value in the bilateral splenium of CC as well as the FA vaue in both left frontal lobe and left CC's splenium.
Lin et al. (2012)	HD: 35 (M/F: 32/3) (37.00±7.96 years) Mean heroin use: 12.4 years (1-24 years) Daily dose of heroin use: 0.1-4.5 g/day Detoxification phase: They entered a methadone maintenance program for an average of 20.3 months. The averaged last dose of methadone was 27.7 mg. Moreover, they were abstinent from opioids during the last	MRI Diffusion Tensor Imaging (DTI) Voxel-based Statistical using Tract-Based Spatial Statistic (TBSS)	HD-CN: The performance of HD in semantic verbal and short-term memory tasks, visual construction and executive function was worse than CN. Furthermore, anxiety and depression scores were higher compared to controls. Decreased FA, increased radial diffusivity, and small or absent reduction in axial diffusivity values have been located in left parahippocampus and cingulate gyrus and left inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF) and uncinate

	year. Nicotine use: >10 cigarettes/day for 24/35 participants Education: 10.71±1.88 years CN: 23 (M/F: 22/1) (34.32±7.45 years) Nicotine use: >10 cigarettes /day for 11/23 participants Education: 15.22 ±1.31 years Many neuropsychological tests have been administered either prior of two days after MRI scanning in order to assess memory functions, language, executive functions, visual construction praxis as well as both anxiety and depression symptoms.		fasciculus as well as in cerebellar peducles bilaterally. Reduced FA and axonal diffusivity but increased radial diffusivity have been reported in left uncinate and right inferior fronto-occipital fasciculus and cerebellum's anterior vermis. HD: The FA value was negatively correlated with depression scores in cingulum, uncinated fasciculus and cerebellar peduncles all in the left cerebrum. Semantic verbal fluency was slightly correlated to the FA values in left SLF, MCP and parahippocampus. Similar pattern has been observed between digit span backward scores and FA values in the former brain regions apart from left parahippocampus. However, negative correlation was reported between digit span forward-backward and FA in left MCP. Finally, FA in left SLC and uncinated fasciculus as well as in right anterior cerebellum has been gently associated with block design scores. The semantic verbal fluency scores negatively associated with white matter density in the left MCP. Radial diffusivity value has been positively correlated with depression scores in the left MCP. However, inverse correlations have been revealed between RD and semantic verbal fluency in the left parahippocampus SLF and MCP. Similarly, negative correlations with digit span backward in the left SLF and block design in the left MCP. However, scores in digit span forward-backward was positively associated in left parahippocampus. The duration of methadone maintenance treatment has been correlated to reduced DTI values in the parahippocampus and SLF in the left hemisphere. However, no significant association has been revealed between DTI measures and both duration and dose of heroin.

Li et al. (2013)	HD:17 (M/F: 17/0) (33.9±6.4 years) Heroin use: 81.5±33.9 months Daily dose of heroin use: not reported Detoxification phase: They were abstinent from heroin for 7.9±2.1 days Nicotine use: 20.0±6.1 (no.cigarettes/day) Education: 10.2±2.8 years CN: 15(M/F: 15/0) (34.3±7.3 years) Nicotine use: 18.3±2.2 (no.cigarettes/day) Education: 10.6 ±2.4 years	MRI Diffusion Tensor Imaging (DTI) Voxel-based analysis	HD<CN: FA reductions have been located in the cingulate gyrus, medial and frontal sub-gyrus bilaterally. Similar pattern has been observed in bilateral extra–nuclear, left temporal sub-gyrus and right superior frontal gyrus. The HD group presented increased radial diffusivity in extra-nuclear, cingulate gyrus and frontal sub-gyrus all bilaterally relative to controls. However, neither increments in radial diffusivity nor differences in axonal diffusivity have been observed. No significant correlations have been observed between duration of heroin or accumulated heroin effect and FA or radial diffusivity values in the brain regions where group differences have been found.
Cerebral Perfusion			
Denier et al. (2013a)	HD:15 (M/F: 9/6) (40.9±6.6 years) Heroin use: 20.5±7.7 years Daily dose of heroin use: 346.0±173.4 mg/day Detoxification phase: They were abstinent from other illicit drugs apart from prescribed heroin. They have been free from alcohol for 72 hours and from smoking for 2 hours before MRI scanning. Each participant has been scanned twice within an interval 9±3.8 days. On one day, they received an intravenous heroin or placebo injection 20 minutes before scanning and the other after the scanning procedure. The participants were randomly assigned to either heroin or placebo group. The psychological effect of the substance induced has been measured by Heroin Craving Questionnaire (HCQ) and the visual analogue scales (VAS). Some of the cohorts (5/15) had an additive substitution receiving a small methadone dose. Nicotine use: smokers but the (no.cigarettes/day) was not reported.	Pharmacological Magnetic Resonance Imaging (phMRI) Pulsed arterial spin labeling (ASL)	HG-PG: The heroin group presented both lower heart rates and blood oxygen saturation. The symptoms remained significant one hour after injection. The psychometric effects such as intoxication, sedation and withdrawal relief were higher in heroin-dependent individuals than the placebo group. The desire for heroin consumption did not differ significantly between groups. Three major clusters of lower perfusion have been observed that are the bilateral insula, the area of medial frontal cortex mainly in the ACC and the medial frontal gyrus. Gender differences in perfusion within the aforementioned clusters have not been mentioned.

	Education: not reported		
Denier et al. (2013b)	HD:14 (M/F: 8/6) (40.7±6.8 years) Heroin use: 21.4±7.2 years Daily dose of heroin use: 352±178 mg/day Detoxification phase: They were abstinent from other illicit drugs apart from prescribed heroin. They have been free from alcohol for 72 hours and from smoking for 2 hours before MRI scanning. Each participant has been scanned twice within an interval 8.4±3.3 days. On one day, they received an intravenous heroin or placebo injection 20 minutes before scanning and the other after the scanning procedure. The participants were randomly assigned to either heroin or placebo group. They received the half of their daily heroin dose in the morning. Nicotine use: not reported Education: not reported	MRI Voxel-based Morphometry Arterial spin labeling (ASL) Multimodal correlation analyses	PG: A positive correlation has been revealed between perfusion and GM volume in frontal regions bilaterally such as the inferior, superior and middle frontal gyrus, the precentral gyrus and the frontal pole as well as in the right paracingulate cortex including ACC parts. HG: Perfusion has been positively associated with GM volume in frontal brain regions such as the inferior and middle frontal gyrus and precentral gyrus in the left hemisphere but also in the frontal pole bilaterally. However, it was linked negatively to the temporal fusiform cortex and the inferior temporal gyrus bilaterally.
Qiu et al. (2011)	HD: 31 (M/F: 26/5) (37.19±7.5 years) Heroin use: 9.35±5.41 years Daily dose of heroin use: 0.6±0.4 g/day Detoxification phase: All the HG individuals were under methadone maintenance treatment. Nicotine use: 19.03±8.604 (no.cigarettes/day) Education: 10.36±3.166 years IGT score: -3.43±5.626 (14/31 participants) CN: 24 (M/F: 20/4) (35.38±6.020 years) Nicotine use: 16.25±9.237 (no.cigarettes/day) Education: 11.21±3.257 years IGT score: 6.29±6.603 (14/24 participants) The remaining participants of	fMRI Regional Homogeneity analysis Voxel-based analysis	HD<CN: Reduced regional homogeneity has been showed in medial OFC, cuneus, dorsal medial thalamus and lingual gyrus all bilaterally. The performance of HD has been worse compared to CN in the IGT task. The mean regional homogeneity in medial OFC and medial dorsal nucleus in the right cerebrum along with the left lingual gyrus and bilateral cuneus has been negatively correlated with the duration of heroin use. In contrary, mean regional homogeneity in the bilateral medial OFC showed positive correlation with IGT performance for both groups.

	each group have not managed to finish the task. The Iowa Gabling Task (IGT) has been used for the assessment of cohorts' decision making during uncertainty.		
Cortical Thickness			
Li et al. (2013a)	HD: 18 (M/F: 17/1) (36.11±5.72 years) Heroin use: 12±5.32 years Daily dose of heroin use: 0.62±0.31 g/day Detoxification phase: All the HG individuals were under methadone maintenance treatment with daily methadone dosage 36.67±28.65g/day. They were abstinent for 6-7 days before scanning and therefore they presented withdrawal symptoms. Nicotine use: 17.78±13.09 (no.cigarettes/day) Education: 9.61±2.75 years CN: 15 (M/F: 12/3) (36.80±8.53 years) Nicotine use: 11.67±12.49 (no.cigarettes/day) Education: 9.20±4.69 years	3-D high resolution Structural MRI Vertex-wise analysis ROI-wise analysis	Vertex-wise Analysis HD-CN: Cortical thickness has been found reduced in the bilateral superior frontal, the right superior/middle temporal and insular and the left caudal middle frontal regions. However, enhanced cortical thickness has been detected in the left superior parietal and temporal pole, in the right lateral occipital and inferior parietal regions as well as in the right cuneus and bilateral lingual gyrus. ROI-wise Analysis HD-CN: Decreased cortical thickness has been showed in left superior frontal, calcarine and tranverse collateral sulcus and in the right lingual and media occipital-temporal sulcus as well as in the left precuneus gyrus and left inferior temporal sulcus. Combining the two approaches, they concluded that cortical thickness alterations located mainly in frontal and occipital brain regions. More precisely, the overlapping regions with reduced cortical thickness have been the left anterior transverse collateral, calcarine and superior frontal sulcus, the left precuneus gyrus as well as the lingual and the medial occipital-temporal sulcus in the right hemisphere.

Table A. 1: Description of the resting-state studies on the functional connectivity, the abnormal topological properties of heroin-dependent individuals and their structural deficits.

Notes: All the participants in the aforementioned studies were right-handed. HD: heroin-dependent; CN: cognitive normal; OD: opiate dependent; PA: prolonged abstinent; HG: heroin group; PG: placebo group; rsFC: resting-state functional connectivity; NAc: nucleus accumbens; ACC: anterior cingulate cortex; OFC: orbital frontal cortex; IFG: inferior frontal gyrus; PFC: prefrontal cortex; IPL: inferior parietal lobule; dACC: dorsal anterior cingulate cortex; vACC: ventral anterior cingulate cortex; rACC: rostral anterior cingulate cortex; PCC: posterior cingulate cortex; CG: cingulate gyrus; CC: cingulate cortex; MCC: middle cingulate gyrus; pC: precuneus; PHG: parahippocampal gyrus; SMC: supplementary motor cortex; ALFF: amplitude of low-frequency fluctuation; FFA: fusiform area; MeFG: medial frontal gyrus; IPC: inferior parietal cortex; ILF: inferior longitudinal fasciculus; SLF: superior longitudinal fasciculus; MCP: cerebellar peduncles; DLPFC: dorsolateral prefrontal cortex; MPFC: medial prefrontal cortex; SMA: supramarginal motor area; iAFC: intrinsic amygdala functional network; DMN: default-mode network; FTND: Fagerstrom Test of Nicotine Dependence; GM: gray matter; WM: white matter; TIV: total incranial fluid; CSF: cerebrospinal fluid; FA: fractional anisotropy; ADC: apparent diffusion coefficient; RD: radial diffusivity.

FIGURE CAPTIONS

Figure 1: Modeling of addicted brain and heroin-induced behavioral traits. A modified representation of the proposed addiction model by Volkow et al., 2003 that involves four interacting and overlapping circuits: the reward circuit, which located in the ventral pallidum and the nucleus accumbens (NAc), the motivation/drive circuit, which is represented by the orbitofrontal cortex (OFC) and the subcallosal cortex, the memory/learning circuit, which is located in the hippocampus and the amygdala and finally control circuit, which is located in the anterior cingulate gyrus (ACC) and the prefrontal cortex. The bold-colored arrows represent an enchanced loop between the memory, reward andmotivation/drive circuits compared to normal whereas the gray-colored arrows are absent in an addicted brain compared to healthy individuals resulting to behavioral traits suchs as impulsivity including risky decision-making and weak reponse inhibition,apathy, aggressive, violent and immoral behaviour, lack of insight into illness as well as abnormal emotional recognition. Modified with permission from Volkow et al. (2003).

Figure 2: Alterations in ALFF in heroin-dependent individuals, compared to healthy individuals. The figure is a representation based on Wang et al. (2013) and Jiang et al. (2011) by using WFU Pick Atlas 3.0.3 where the red-colored brain regions (angular gyrus, cerebellum, PCC/ pC, supramarginal gyrus all bilaterally; middle frontal gyrus, superior temporal and occipital gyrus in the left cerebrum) showed enhanced ALFF in heroin-dependent individuals. The blue-colored brain regions (dACC, medial OFC bilaterally; left DLPFC, middle and inferior temporal gyrus as well PCC and cuneus; superior middle frontal cortex, caudate in the right hemisphere) exhibited reduced ALFF in heroin-dependent individuals. The areas where the two colors overlap refer to areas with controversial findings.

Figure 3: Brain regions with higher degree in heroin dependent individuals, compared to healthy individuals. The aforementioned brain regions (bilateral OFC, precuneus, rostral part of ACC, cerebellum, putamen, parahippocampal gyrus and dorsolateral part of frontal cortex; thalamus, PCC, caudate, inferior and medial frontal cortexin the left hemisphere and right middle aspect of temporal gyrus) were characterized as highly connected brain regions in heroin-dependent subjects based on the findings reported by Yuan et al., 2010c. In particular, left precuneus and postcentral gyrus as well as right middle aspect of frontal gyrus were reported as heroin-specific hubs by Jiang et al. 2013. The figure was designed by using WFU Pick Atlas 3.0.3.