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Nature of functional links in valuation networks differentiates impulsive behaviors between abstinent heroin-dependent subjects and nondrug-using subjects

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ABSTRACT

Advanced neuroimaging studies have identified brain correlates of pathological impulsivity in a variety of neuropsychiatric disorders. However, whether and how these spatially separate and functionally integrated neural correlates collectively contribute to aberrant impulsive behaviors remains unclear. Building on recent progress in neuroeconomics toward determining a biological account of human behaviors, we employed resting-state functional MRI to characterize the nature of the links between these neural correlates and to investigate their impact on impulsivity. We demonstrated that through functional connectivity with the ventral medial prefrontal cortex, the δ-network (regions of the executive control system, such as the dorsolateral prefrontal cortex) and the β-network (regions of the reward system involved in the mesocorticolimbic pathway), jointly influence impulsivity measured by the Barratt impulsiveness scale scores. In control nondrug-using subjects, the functional link between the β- and δ-networks is balanced, and the δ-network competitively controls impulsivity. However, in abstinent heroin-dependent subjects, the link is imbalanced, with stronger β-network connectivity and weaker δ-network connectivity. The imbalanced link is associated with impulsivity, indicating that the β- and δ-networks may mutually reinforce each other in abstinent heroin-dependent subjects. These findings of an aberrant link between the β- and δ-networks in abstinent heroin-dependent subjects may shed light on the mechanism of aberrant behaviors of drug addiction and may serve as an endophenotype to mark individual subjects' self-control capacity.

Introduction

Aberrant behaviors related to impaired self-control have been observed in a variety of neuropsychiatric disorders, including substance addiction (Baler and Volkow, 2006), pathological gambling (Limbrick-Oldfield et al., 2013), and ADHD (Sonuga-Barke and Fairchild, 2012). Advanced neuroimaging studies identifying brain correlates of impulsivity may provide insights into the nature of these aberrant self-control behaviors. Interestingly, the brain correlates underlying these disorders bear striking similarities. For example, it is well documented that drug addicts, pathological gamblers and ADHD subjects exhibit high impulsivity reflected by steep value discounting. This elevated impulsivity is usually correlated with weak top-down executive neural networks (including brain regions such as the DLPFC), and with hypersensitive reward networks (including brain regions such as OFC, dorsal striatum, thalamus, vmPFC, and NAcc) (Lawrence et al., 2009; Limbrick-Oldfield et al., 2013; Peters and Büchel, 2011; Sonuga-Barke and Fairchild, 2012). Obesity also shows significant functional abnormalities

Abbreviations: 3D-SPGR, three-dimensional spoiled gradient-recalled echo; ADHD, attention deficit hyperactivity disorder; AFNI, Analysis of Functional NeuroImages (software); ANCOVA, analysis of covariance; BIS, Barratt impulsiveness scale; CC, cross-correlation coefficient; CN, control nondrug-using; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsal medial prefrontal cortex; DSM-IV, diagnostic and statistical manual of mental disorders, 4th edition; EPI, echo planar imaging; FC, functional connectivity; FOV, field of view; FWHM, full width at half maximum; GM, gray matter; HD, heroin-dependent; iBOLD, intrinsic spontaneous blood oxygen level-dependent; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; LOO, leave-one-out; MNI, Montreal Neurological Institute; NAcc, neucleus accumbens; o-VBM, optimized voxel-based morphometric; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; ROI, region of interest; SCID, structured clinical interview for DSM-IV; SPM8, statistical parametric mapping, version 8 (Matlab package); TE, echo time; TR, repetition time; vmPFC, ventral medial prefrontal cortex; WM, white matter.

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in discrete brain regions, especially in the ventral and dorsal striatal networks (Volkow et al., 2012; Tomasi and Volkow, 2013). Similar to the above findings, Shannon et al. demonstrated that the functional connectivity of the default mode and attention/control networks may predict juvenile offenders' impulsivity (Shannon et al., 2011). These converging results strongly suggest that many aberrant behaviors that are associated with impaired self-control may be supported by competing interactions between the reward networks and the executive control networks (Bechara, 2005; Bickel et al., 2007; Monterosso and Piray, 2012; Peters and Büchel, 2011).

However, less is known about the competing mechanisms among these networks. In particular, it is not well understood how these regionally separate yet functionally integrated brain correlates interact, and how these interactions further result in aberrant behavioral manifestations. Previous studies demonstrated that, in a single-valuation network model, the major regions of the valuation network were the vmPFC, OFC, and striatum (Kable and Glimcher, 2007, 2009). In contrast to the single-valuation network model, McClure et al. proposed a dual-valuation network model (McClure et al., 2004, 2007). In this model, the valuation network is defined as a "β-network" for mediating the short-term or immediate value, whereas the executive control systems are defined as a "δ-network", which modifies the long-term value. Hare et al. proposed a self-control model (Hare et al., 2009) and more research results suggested that the executive control system (involving the DLPFC and parietal cortex) modulates the valuation network (including the OFC, striatum, thalamus and vmPFC) (Bartra et al., 2013; Baumgartner et al., 2011; Figner et al., 2010; Peters and Büchel, 2011; Steinbeis et al., 2012). These studies advanced the single- and dual-valuation models and suggested that although the β- and δ-valuation networks are spatially separate and functionally distinct, they are integrated to determine valuation. Nevertheless, the question remains as to why the δ-network, when confronted with a decision or choice, can exert its modulating function over the β-network in healthy people, but not in subjects with aberrant self-control behaviors. Indeed, it is simply not clear how the β- and δ-valuation networks are linked to bias the preference in individuals with aberrant self-control behavior.

This study assessed these valuation networks using resting-state functional MRI with the vmPFC as a connective node or a "seed" region. The selection of the seed region is based on the critical functions of vmPFC in the valuation network. The vmPFC plays a significant role in encoding and integrating subjective value signals, in assigning and optimizing decision-making processes, and in coordinating and evaluating the significance of alternative rewards (Bartra et al., 2013; Grabenhorst et al., 2011; Hare et al., 2009, 2010; Kable and Glimcher, 2007, 2009). We focused on characterizing β- and δ-network features and on investigating the nature of their links in heroin-dependent (HD) and control nondrug-using (CN) subjects to test our hypothesis that alterations exist in the natural links between the β- and δ-networks in heroin addiction, and that these alterations are associated with exhibited impulsivity.

Materials and methods

Participants

Thirty abstinent HD subjects were recruited from Beijing Ankang Hospital (Beijing, China), and 20 CN subjects also participated in this study. Both participant groups consisted of right-handed males, of normal intelligence, who were well-matched for age and years of education. Inclusion and exclusion criteria for heroin abusers and control subjects were described previously (Fu et al., 2008). In summary, each HD subject met DSM-IV criteria for heroin dependence, used heroin for more than two years, and was abstinent for at least two weeks. They also tested negative for morphine through urinalysis and negative for HIV in a blood test. None of the subjects had a history of neurological or psychiatric diseases, seizures, or head injury. None of the subjects were shown to have other structural abnormalities by an anatomical MRI scan. Two experienced psychiatrists assessed the inclusion and exclusion process, in accordance with the SCID. The study was approved by the Research Ethics Committee of Beijing Ankang Hospital and Beijing Institute of Basic Medical Science. The entire experiment was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all individual subjects prior to the study. Eight HD and five CN subjects were excluded from this study due to excessive motion artifacts (i.e., translational movement exceeded 1 mm or more than 1° rotational movement), thus leaving 22 and 15 subjects in the HD and CN groups, respectively, for further analysis.

Behavioral measurement

The BIS-11 (Chinese version) was employed to assess study subjects' impulsivity (Patton et al., 1995). The BIS-11 has 30 4-point Likert-type items, which provide an overall total score and three subscale scores for Attention, Motor and Nonplanning impulsiveness. Higher scores signify higher impulsivity.

MRI acquisition

MR images were acquired by a 3 T Signa GE scanner with a standard quadrature transmit and receive head coil. The whole-brain resting-state fMRI data was acquired with a single-shot gradient-recalled EPI sequence, and the scanning parameters were as follows: TE of 25 ms, TR of 2 s, flip angle of 90°, 20 slices, slice thickness of 5 mm (with an additional 1-mm gap space), imaging matrix size of 64 × 64, FOV of 24 cm × 24 cm. All 180 time points of images were collected in 6-minute resting scans without task performance. All subjects were instructed to not fall asleep, keep their heads still, and close their eyes. We also acquired high-resolution anatomical images of each individual subject, using a T1-weighted 3D-SPGR pulse sequence with the following scanning parameters: TE of 4.8 ms, TR of 10.4 ms, flip angle of 15°, 140 slices without spacing, slice thickness of 1 mm, matrix size of 256 × 256, FOV of 24 cm × 24 cm. In addition, we also recorded each subject's cardiac and respiratory signals for physiological noise corrections during image preprocessing.

Image preprocessing

All imaging data preprocessing and functional synchrony analyses were conducted using the AFNI software (http://afni.nimh.nih.gov/afni/), and the SPM8 package (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) on Matlab platform. For imaging preprocessing, the first five dataset volumes were discarded due to the T1 nonequilibrium effect, then slice timing correction and volume registration (*3dvolreg*, *AFNI*), linear detrend (*3dDetrend*, *AFNI*), and physiological noise correction for respiratory and cardiac signals (*3dretroicor* and *3dDeconvolve*, *AFNI*) were performed. Also, noise from WM, CSF, global signal and six-way motion vectors was regressed out (*3dDeconvolve*, *AFNI*). A band-pass filter was then applied to keep the low-frequency fluctuations between 0.015 Hz and 0.1 Hz (*3dFourier*, *AFNI*) (Fox and Raichle, 2007; Fransson, 2005).

Statistical analysis

Structural image analysis

An o-VBM analysis was conducted using SPM8 (Good et al., 2001) to calculate the GM volume of subjects within each group. All subjects' individual T1-weighted 3D-SPGR images were first segmented into three parts — GM, WM, and CSF. The segmented GM was then normalized into MNI space. Meanwhile, the anatomical images were also normalized into MNI space, using the deformation field generated by the normalization of GM. The normalized anatomical images were