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The relationship between the striatal dopamine transporter and novelty seeking and cognitive flexibility in opioid dependence

Chih-Sung Liang [a,b], Pei-Shen Ho [b], Che-Hung Yen [a,c], Chun-Yen Chen [a,d], Shin-Chang Kuo [a,d], Chang-Chih Huang [a,e], Yi-Wei Yeh [a,d], Kuo-Hsing Ma [f], San-Yuan Huang [a,d,*]

[a] Graduate Institute of Medical Sciences, National Defense Medical Center, Taipei, Taiwan, ROC
[b] Department of Psychiatry, Beitou Branch, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC
[c] Department of Neurology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC
[d] Department of Psychiatry, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC
[e] Department of Psychiatry, Taipei Branch, Buddhist Tzu Chi General Hospital, Taipei, Taiwan, ROC
[f] Department of anatomy and biology, National Defense Medical Center, Taipei, Taiwan, ROC

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ABSTRACT

Novelty seeking (NS) is a core personality trait that primes the susceptibility to drug addiction. Striatal dopamine activity contributes to cognitive flexibility, an important cognitive strategy to inhibit impulsivity and compulsive drug-seeking behavior. Evidence supports the association between dopamine and NS. Opioid-dependent patients show higher levels of NS, and repeated opioid exposure can cause cognitive deficits including poor cognitive flexibility and impaired impulse control. However, in opioid-dependent patients, the link between NS, striatal dopamine activity, and cognitive flexibility is still unclear. We recruited 22 opioid-dependent individuals and 30 age- and sex-matched healthy controls. Single-photon emission computed tomography with [^{99m}Tc]TRODAT-1 as a ligand was used to measure the striatal dopamine transporter (DAT) availability. The Trail Making Test (TMT) was performed to assess cognitive flexibility. Cloninger's Tridimensional Personality Questionnaire (TPQ) was used to measure NS. We found that in opioid-dependent patients, the striatal DAT availability was lower and negatively associated with TMT Part B ÷ Part A. Moreover, an inverted-U shape significantly matched the scores of NS as a function of the striatal DAT availability, with maximum NS potential in the midrange of the DAT availability. An extra sum-of-squares *F* test was conducted, indicating that a quadratic model fitted the association between the DAT and NS better than a linear model did. In brief, in opioid-dependent patients, the striatal DAT availability is nonlinearly linked to NS and linearly linked to cognitive flexibility. The role of the striatal DAT in the transition from controlled to compulsive opioid use warrants further research.

1. Introduction

The conceptualization of drug addiction has undergone a remarkable transformation in recent decades. Evidence continues to accumulate indicating that neurobiological brain perturbations associated with addictive drugs may persist beyond detoxification (Kauer and Malenka, 2007; Luscher and Malenka, 2011; Nestler, 2001). With repeated drug exposure, the reward circuits of the brain are hijacked and rewired, leading to long-lasting cognitive, psychological, and behavioral symptoms (Kauer and Malenka, 2007; Luscher and Malenka, 2011; Nestler, 2001). The recognition that addiction is a chronic relapsing disorder indeed facilitates more sophisticated treatment strategies, and researchers have focused on determining what renders some individuals more vulnerable to drug addiction. Novelty seeking (NS), one of the temperament dimensions of personality, is now considered as a key predisposing factor (Wingo et al., 2015).

NS refers to a tendency to be aroused by appetitive or novel stimuli and to respond to them positively (Cloninger, 1987). High novelty seekers are characterized by extraversion, impulsivity, fickleness, disorderliness, frequent exploratory activity in pursuing potential rewards, and active avoidance of monotony and punishment (Cloninger, 1987). Substantial evidence from animal and human studies indicates that NS can predict the propensity and severity of compulsive drug use (Arenas et al., 2016; Belin et al., 2011; Ersche et al., 2012; Robbins et al., 2012; Wingo et al., 2015). Moreover, researchers suggests NS as a behavioral endophenotype of addiction and have investigated the neurobiological underpinning of NS (Dagher and Robbins, 2009; Jupp and Dalley, 2014; Wingo et al., 2015). Among potential neural substrates, dopamine clearly links NS and drug addiction as both conditions highly

* Corresponding author at: Department of Psychiatry, Tri-Service General Hospital, National Defense Medical Center, No. 325, Chenggong Road, Sec. 2, Nei-Hu District, Taipei 114, Taiwan, ROC.
E-mail address: hsy@ndmctsgh.edu.tw (S.-Y. Huang).

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involve central dopaminergic neurotransmission (Dagher and Robbins, 2009; Jupp and Dalley, 2014; Wingo et al., 2015).

Opioids are extremely addictive, and previous studies have reported higher NS in opioid-dependent patients (Demetrovics et al., 2010; Gerra et al., 2000; Lee et al., 2013). Like other addictive drugs, opioid-dependent patients have lower levels of striatal D2 receptors and higher dopamine release after cue-exposure (Zijlstra et al., 2008). However, some authors suggest that the manner in which dopamine functions and influences the pathogenesis of opioid dependence is different from that of other addictive drugs (Badiani et al., 2011; Nutt et al., 2015). Indeed, research on opioids has not consistently replicated the common characteristics of addiction to psychostimulants. For example, human studies revealed that striatal dopamine release did not occur in opioid-dependent patients when they were expecting opioid rewards (Watson et al., 2014) and after opioid was injected (Daglish et al., 2008). An animal study found that lower levels of striatal dopamine D2/3 receptors did not predict opioid self-administration (McNamara et al., 2010). Interestingly, recent neuroimaging studies that investigated the role of the striatal dopamine transporter (DAT) yielded seemingly converging evidence — remarkably lower striatal DAT availability in opioid-dependent patients (Liang et al., 2016; Lin et al., 2015; Yeh et al., 2012; Yuan et al., 2015). Moreover, previous animal studies have suggested that DAT serves to not only terminate dopamine signaling but also maintain normal dopamine homeostasis and function (Giros et al., 1996; Jones et al., 1998; Jones et al., 1999). However, so far, no neuroimaging study has examined the association between the DAT and NS in this population.

A meta-analysis (Baldacchino et al., 2012) and a systemic review (Lundqvist, 2005) indicated that chronic opioid exposure can cause neurocognitive deficits in working memory, cognitive impulsivity, and cognitive flexibility. For opioid-dependent patients, it may be tempting to believe that high NS precedes neurocognitive deficits. However, from a developmental perspective, emotional, behavioral, and cognitive response patterns can shape individual temperament (Henderson and Wachs, 2007). For example, retaining information in memory over a brief period, an ability which relies on frontal lobe function, may represent a general contributor to perseverance for a long-term goal and decreased impulsivity (Miller and Cohen, 2001). Therefore, high NS in opioid-dependent patients might be not only an inherent part of temperament but also enhanced after chronic opioid exposure. The interdependent nature of temperament and cognition implies overlapping neural substrates. At a neurocircuitry level, optimal dopamine levels in the prefrontal cortex promote cognitive stability, while optimal dopamine levels in the striatum facilitate flexibility in response to novel information (Cools and D'Esposito, 2011). Therefore, exploring the associations between deficits in cognitive flexibility, NS, and striatal DAT availability might improve our understanding of the transition from controlled to compulsive opioid use.

The principal aim of this study was to resolve the following questions. First, was there an association between reduced striatal DAT availability and high NS in opioid-dependent patients? Second, did the striatal DAT availability correlate with deficits in cognitive flexibility? Third, did NS play a role in the link, if any, between striatal DAT availability and cognitive flexibility? Answering these questions may help to tease out the neurobiological substrates that underlie these important psychopathological domains.

2. Methods and materials

2.1. Participants

Between 2010 and 2014, participants who sought treatment for heroin addiction at the Tri-Service General Hospital, National Medical Defense Center, Taiwan, were considered eligible for participation in the study. Written informed consent was obtained in accordance with the National Health and Medical Research Council guidelines. All participants were fully informed regarding the aims and details of the study and were free to withdraw their consent at any time. The Institutional Review Board for the Protection of Human Subjects at the Tri-Service General Hospital approved the protocol. An experienced psychologist interviewed all participants using the Chinese version of the modified Schedule for Affective Disorders and Schizophrenia-Lifetime to screen their psychiatric conditions (Endicott and Spitzer, 1978). A psychiatrist with over 20 years of clinical experience again confirmed the diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (American Psychiatric Association. and American Psychiatric Association. Task Force on DSM-IV., 2000). All participants were required to be between 20 and 60 years of age and in good health. Individuals were excluded if they had a history of nicotine dependence, mental retardation, neurodevelopmental disorders, neurodegenerative disorders, neurological disorders, movement disorders, eye diseases, traumatic head injury with loss of consciousness, comorbid psychiatric disorders, major medical conditions, and other conditions that can alter cerebral functioning. As a result, we recruited 22 male opioid-dependent patients and 30 age- and sex-matched healthy controls.

2.2. Personality trait assessment

A well-trained and experienced psychologist administered the cognitive and psychological tests to participants on the same day as the neuroimaging scans. A Chinese version of the Cloninger's Tridimensional Personality Questionnaire (TPQ) was used, which is a self-administered instrument measuring three distinct personality dimensions — NS, harm avoidance (HA), and reward dependence. The reward dependence dimension was excluded because of low internal consistency among the Han Chinese population in Taiwan (Cronbach's $\alpha = 0.54$) (Chen et al., 2002). The NS (32 items, Cronbach's $\alpha = 0.70$) and HA (34 items, Cronbach's $\alpha = 0.87$) dimensions were analyzed. The severity of opioid dependence was represented by the duration of opioid use. The psychologist was blind to the study protocol.

2.3. Cognitive flexibility battery

The Trail Making Test (TMT) A and B, a widely used instrument in neuropsychological assessment, provides information about visuoperceptual abilities, working memory, and cognitive flexibility (Sanchez-Cubillo et al., 2009). The TMT comprises the TMTA and TMTB. The TMTA requires the participants to connect 25 randomly positioned numbers on a page in consecutive order. The TMTB requires the participants to connect a series of randomly positioned numbers and animal sequences from the Chinese zodiac interchangeably, such as 1–Rat–2–Ox–3–Tiger… 12–Pig. This modification has been widely used in older adults or poorly educated Chinese people who are unfamiliar with English. The direct score of each part represents the amount of time to complete the task under time pressure. The B − A difference score and B/A ratio were calculated. Evidence clearly indicates that the TMTB results reflect the ability of working memory and set switching (also referred to as cognitive flexibility), TMTB − A provides a relatively pure indicator of executive control (Arbuthnott and Frank, 2000; Sanchez-Cubillo et al., 2009), and larger TMTB/A ratio captures the domain of impaired cognitive flexibility (Arbuthnott and Frank, 2000).

2.4. Striatal dopamine transporter availability

The radiotracer [^{99m}Tc]TRODAT-1 is an imaging agent for the striatal DAT with high affinity and selectivity, and the striatal DAT availability was assessed with single-photon emission computed tomography (SPECT). Opioid-dependent patients continued to use heroin and experienced no withdrawal or intoxication symptoms. The self-report of last use of heroin prior to SPECT scanning was within 24 h, which was verified by a urine drug screen showing positive for opioids only. Healthy controls were not taking any medications that could affect the central