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Right inferior frontal cortex activity correlates with tolcapone responsivity in problem and pathological gamblers

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ABSTRACT

Failures of self-regulation in problem and pathological gambling (PPG) are thought to emerge from failures of top-down control, reflected neurophysiologically in a reduced capacity of prefrontal cortex to influence activity within subcortical structures. In patients with addictions, these impairments have been argued to alter evaluation of reward within dopaminergic neuromodulatory systems. Previously we demonstrated that augmenting dopamine tone in frontal cortex via use of tolcapone, an inhibitor of the dopamine-degrading enzyme catechol-O-methyltransferase (COMT), reduced delay discounting, a measure of impulsivity, in healthy subjects. To evaluate this potentially translational approach to augmenting prefrontal inhibitory control, here we hypothesized that increasing cortical dopamine tone would reduce delay discounting in PPG subjects in proportion to its ability to augment top-down control. To causally test this hypothesis, we administered the COMT inhibitor tolcapone in a randomized, double-blind, placebo-controlled, within-subject study of 17 PPG subjects who performed a delay discounting task while functional MRI images were obtained. In this subject population, we found that greater BOLD activity during the placebo condition within the right inferior frontal cortex (RIFC), a region thought to be important for inhibitory control, correlated with greater declines in impulsivity on tolcapone versus placebo. Intriguingly, connectivity between RIFC and the right striatum, and not the level of activity within RIFC itself, increased on tolcapone versus placebo. Together, these findings support the hypothesis that tolcapone-mediated increases in top-down control may reduce impulsivity in PPG subjects, a finding with potential translational relevance for gambling disorders, and for behavioral addictions in general.

1. Introduction

Impulsivity is a well-known correlate of addiction (Bickel et al., 2014). The tendency to choose smaller but immediate rewards over larger but delayed ones is greater in subjects with substance use disorders than in matched controls (Bickel and Marsch, 2001), and the prototypical behavioral addiction, pathological gambling, is likewise associated with steep discounting of delayed rewards (Wiehler and Peters, 2015). This increase in delay discounting has been linked to dysregulation of dopamine-based neuromodulatory systems (Volkow and Baler, 2015), which in turn have been associated with the addictive disorders themselves. For example, D2/D3 dopamine agonists are strikingly associated with the induction of problem and pathological gambling (PPG) in Parkinson's disease (Voon et al., 2009). As PET and other neuroimaging studies have begun to reveal changes both in the activation of reward circuitry (Balodis et al., 2012) and striatal dopamine measures (Joutsa et al., 2015; Linnet et al., 2011) in patients with PPG, disorders along the behavioral addiction spectrum, including PPG, are now considered to share many features with other addictions. However, because such behavioral addictions may be less confounded by use of psychoactive substances, they can potentially provide a unique opportunity to understand the role of dopamine in addictive disorders more broadly.

It has recently been suggested that the particular locus of dopamine dysregulation may be important to understanding addictive disorders (Kayser et al., 2012; Volkow and Baler, 2015), and specifically that cortical and striatal dopamine might differentially impact behaviors such as impulsivity. In part, these ideas arise from the finding that dopamine metabolism is known to be regulated differentially in the frontal cortex and striatum: while termination of dopamine's effect in the striatal synapse is primarily mediated by reuptake via the dopamine transporter, the action of synaptic dopamine in the frontal cortex is terminated primarily via degradation by the catechol-O-methyltransferase (COMT) enzyme (Chen et al., 2004; Gogos et al., 1998). We therefore reasoned that the COMT antagonist tolcapone might preferentially augment

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cortical dopamine tone (Tunbridge et al., 2004) and reduce impulsivity via increased activity within cognitive control regions, similar to its effects on aspects of working memory (Apud et al., 2007). In healthy controls, our previous work demonstrated that this prediction held (Kayser et al., 2012), particularly for subjects with greater baseline impulsivity as measured by the Barratt Impulsiveness Scale (BIS). Similarly, an open-label study of tolcapone without a placebo control in patients with gambling disorders suggested that changes in frontoparietal brain activity during performance of a Tower of London task (a task to assess planning) on tolcapone correlated with changes in patients' scores on the Yale Brown Obsessive Compulsive Scale Modified for Pathological Gambling (PG-YBOCS) across time (Grant et al., 2013). Conversely, Pine and colleagues demonstrated that healthy subjects given the dopamine precursor L-dopa, which should act throughout the brain, showed consistent increases in delay discounting (Pine et al., 2010). This distinction between frontal and striatal dopamine, possibly due to their time courses (tonic versus phasic, respectively) or their competing influences on frontostriatal "top-down" circuitry, has been suggested to define a potential mechanism for biasing decisions toward later versus sooner choices (Volkow and Baler, 2015).

Complicating the above is the importance of individual differences, and the related knowledge that PPG and other addictive disorders are very likely syndromic – i.e. that diverse etiologies may give rise to a common phenotype that is unlikely to respond in the same manner to a given intervention. Efforts to define a vulnerability phenotype may therefore help to predict treatment response, in keeping with increasing clinical interest in "precision" (or personalized) medicine (Jameson and Longo, 2015). Previous work has argued for the importance of neural phenotypes in particular, with candidate regions derived from cognitive neuroscience research (Ekhtiari et al., 2016). For PPG, putative neural signatures have been identified in reward-related structures including the nucleus accumbens and striatum, as well as in frontal regions thought to be important for valuation (e.g. ventromedial prefrontal cortex) and cognitive control (lateral prefrontal cortex) (Potenza, 2014).

Here we sought to evaluate individual differences in, and potential neural correlates for, the response of PPG subjects to tolcapone. Using reductions in impulsive choice on a delay discounting task as a behavioral assay, we reasoned that specific subjects who demonstrated such reductions would be sensitive to medication-induced increases in cortical dopamine tone. Such sensitivity would be accompanied by changes in the function of prefrontal cognitive control regions, which should consequently exert greater influence over subcortical structures. We thus hypothesized that tolcapone response should correlate with activity within cognitive control regions of the lateral frontal cortex, and that the connectivity of these lateral frontal areas with subcortical structures should increase in proportion to the reduction in delay discounting.

2. Materials and methods

2.1. Subject population

Using advertisements placed via a community-based recruitment tool (Craigslist), we screened 39 subjects, 19 of whom were found to have South Oaks Gambling Scale (SOGS) scores ≥ 5 (mean 10.5 ± 3.4 (sd), range 6–18) as well as no history of medical, psychiatric, or neurological contraindications, and were therefore eligible to participate in the study (Fig. 1). Two subjects were subsequently excluded: one after he failed a urine toxicology screen at his first MRI visit, and another after she fell asleep during her second fMRI session. All subjects gave written informed consent in accordance with the Declaration of Helsinki and the Committee for the Protection of Human Subjects at the University of California, San Francisco and University of California, Berkeley; they were compensated for their participation. Ages ranged from 20 to 47 years old (31.5 ± 8.9 (sd)); 6 of 17 were female (Table 1). Subjects first underwent a history and physical exam, as well as blood testing for liver function and urine screening for drugs of abuse (see below), to ensure that there were no medical contraindications to tolcapone use or MRI scanning. All subjects had normal neuroanatomy as reviewed by a neurologist (A.S.K.), were right-handed, and had normal or corrected-to-normal vision. Before scan sessions, subjects were briefly trained on the delay discounting task in order to familiarize them with task procedures. Subjects then underwent two separate 1.5-h fMRI sessions, each consisting of 6 task runs of 33 trials each for a total of 198 trials, along with one resting state run (which was not further evaluated in this study). Each of the 6 task runs lasted approximately 9 min, with breaks in between to reduce fatigue.

In addition to the requirements for gambling behavior as assessed by the SOGS, inclusion criteria required that subjects be between 18 and 50 years old, right-handed, in generally good health, able to read and speak English, and able to provide informed consent. Women of reproductive age were required to be using an effective form of contraception, and to be neither pregnant nor lactating during study participation. Subjects were excluded if they demonstrated a positive urine drug toxicology screen before any visit, showed an alcohol level greater than zero as measured by breathalyzer before any visit, or reported using psychoactive substances (including both prescription medications and drugs of abuse) within the prior two weeks, or drugs of abuse more than ten times in the previous year. In addition, subjects with a current dependence on marijuana, or who had experienced any previous medical complications of marijuana use, were not eligible; otherwise, subjects could use marijuana no more than three times per week and were required to refrain from marijuana use for at least 48 h prior to testing sessions. These criteria did not apply to nicotine; the two subjects who were regular smokers were both easily able to refrain for the duration of MRI scanning and otherwise continued their regular use. Subjects who were taking medications with dopaminergic, serotonergic, or noradrenergic actions (although animal work suggests that tolcapone induces increases in dopaminergic but not noradrenergic concentrations (Tunbridge et al., 2004)), or who had a known allergy to either tolcapone or the inert constituents in tolcapone capsules, were also excluded. Similarly, after completion of the Mini International Neuropsychiatric Interview (Sheehan et al., 1998), subjects who met screening criteria for an Axis I psychiatric disorder other than gambling disorder, such as major depression, or who had a significant medical or psychiatric illness requiring treatment, were excluded from participating. Because tolcapone carries the potential for hepatotoxicity, liver function tests were required to be no more than three times the upper limit of normal. Finally, subjects were required to be free of MRI contraindications.

Using a random number generator, one of the authors (J.M.M.) randomized consecutive subjects to receive either placebo or tolcapone on their first session, and the other treatment on their second session. Blinded drug assignments were listed as either "A" or "B". Beyond the planning of the study, J.M.M. did not otherwise participate until she contributed to writing the manuscript once the blind had been broken at study completion. All other authors of the paper, as well as the subjects, were blinded to study drug assignments throughout. Because tolcapone might discolor the urine (and therefore might inadvertently unmask drug assignments), the B-vitamin riboflavin was added to both tolcapone and placebo capsules in order to conceal this effect.

2.2. Sample size and randomization

Power analyses for fMRI studies rely upon assumptions about BOLD signal amplitude, smoothness, brain location, and other factors that render principled a priori designations difficult. Based upon empirical, systematic MRI analyses indicating that fMRI studies generally reach good replication at approximately 20 subjects (Desmond and Glover, 2002; Thirion et al., 2007), we targeted this number of participants. Given the challenges inherent in studying this patient population, as well as the financial and temporal constraints of pharmacological fMRI studies,