Personality and Individual Differences 90 (2016) 321–325

Contents lists available at ScienceDirect

Personality and Individual Differences

journal homepage: www.elsevier.com/locate/paid

Pharmacological manipulation of impulsivity: A randomized controlled trial

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ARTICLE INFO

Article history:
Received 23 May 2015
Received in revised form 31 October 2015
Accepted 13 November 2015
Available online 26 November 2015

Keywords:
Impulsivity
Self-control
Cognitive enhancement
Modafinil

ABSTRACT

Impulsivity is a trait that is closely linked to addiction, which has been studied in personality, psychiatry and more recently in the neurocognitive arena. Recently, even obesity has been compared to food addiction with the connotation that obese individuals are impulsive in their behavior. This research is a conceptual review of the construct of impulsivity identified inhibitory control and temporal discounting as two key behavioral constructs universal to all key fields of impulsivity research. This research aimed to identify the modifiability of impulsivity through neuronal dopamine pathways through the use of two pharmaceutical agents, modafinil and atomoxetine. A randomized controlled trial design was executed to test the aforementioned neurocognitive enhancement agents (n = 20 participants receiving atomoxetine and n = 20 participants receiving modafinil) against a placebo (n = 40) in normal weight adults. The results showed that modafinil but not atomoxetine was effective in reducing deficits in inhibitory control. These findings highlight the multiconstruct nature of impulsivity and the need for psychometric tests, which capture these constructs better.

1. Introduction

Impulsivity has been shown to predict as well as act as a modifiable variable in weight loss. Impulses can be defined as a series of urges that result in a reward or consumption and can directly lead to impulsive behaviors. The term impulsivity is the overall trait-like propensity within an individual to engage in such behaviors, and it may be attributed to unusually strong impulses or alternatively with the low ability to reason with or control impulsive actions (Evenden, 1999; Jentsch & Pennington, 2014). Research by Sharma et al. (2014) suggests that impulsivity as a train may not be a single dimension construct, and they show through a meta-analytical principal-components factor analysis that there are broader, higher order personality factors directly linked to impulsivity including neuroticism/negative emotionality, disinhibition versus constraint/conscientiousness and extraversion/positive emotionality/sensation seeking (Sharma, Markon, & Clark, 2014). In a recent study, Murphy et al. suggest that impulsive behavior may not necessarily be associated with obesity but impulsive behaviors can lead to food addiction, which in turn may be the driving force behind higher Body Mass Indexes (BMIs) found in this group (Murphy, Stojek, & MacKillop, 2014). In humans, palatable food is associated with dopamine release in mesolimbic regions, which is similarly found in response to the administration of many addictive substances (Volkow & Wise, 2005). Additionally, obesity has been linked to a reduction in dopamine D_2 receptors, and this factor is also present in individuals with other established addictions. Subjective reward has been reported from eating palatable food and is directly correlated with the resulting degree of dopamine release (Stice, Spoor, Bohon, & Small, 2008; Wang et al., 2001).

In an attempt to delineate the neuronal pathways associated with impulsivity, the action of two clinically approved pharmacological agents for impulsive conditions was tested (Maziade et al., 2009; Schmaal et al., 2013; Wehmeier et al., 2012). Both modafinil and atomoxetine have been licensed for use in adults and children with Attention Deficit/Hyperactivity Disorder (ADHD), a condition characterized by deficits in response inhibition, which is thought to be a surrogate marker of impulsivity. Behavioral laboratory measures of impulsivity have shown children with ADHD to be more impulsive than a normal comparison group (Sykes, Douglas, & Morgenstern, 1973). The use of psychostimulants to treat ADHD and conduct disorder supports the role of neuronal dopamine pathways in their aetiology. The research aims to look at the effects that modafinil and atomoxetine have in reducing deficits in inhibitory control. By determining this link, clinical applications of this treatment may have direct treatment effects in obesity, gambling addictions and other conditions where inhibitory control is involved.

1.1. Modafinil

Modafinil has a clinical profile unique compared with other conventional stimulants, and it is approved by the Federal Drug Agency (FDA) for use in narcolepsy, shift work disorder and excessive daytime sleepiness. Modafinil has been shown to enhance cognition in a variety of disorders such as alcohol dependence (Schmaal et al., 2014), schizophrenia

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http://dx.doi.org/10.1016/j.paid.2015.11.025
0191-8869/

(Hunter, Ganesan, Wilkinson, & Spence, 2006), ADHD (Turner, Clark, Dowson, Robbins, & Sahakian, 2004) and in healthy individuals (Greely et al., 2008; Joos, Docx, Schmaal, Sabbe, & Dom, 2010). Unlike other psychostimulants such as amphetamines and methylphenidate that act through the catecholamine pathways, the mechanism of modafinil is unclear. (Biederman & Pliszka, 2008; Tahsili-Fahadan, Carr, Harris, & Aston-Jones, 2010). However, the drug is reported to affect a number of neurotransmitter systems including dopamine, norepinephrine, 5-hydroxytryptamine, glutamate, GABA, histamine, and orexin. Additionally, the excitatory effects of modafinil may be linked to the disinhibition of excitatory networks, which is caused by the increased electrical coupling and simultaneous decreased input resistance in those neurons that are already electrically coupled (Zolkowska, Andres-Mach, Prisinzano, Baumann, & Luszczki, 2015).

Modafinil has been shown to have an effect on response inhibition that is dependent on baseline impulsivity, and the drug has only shown efficacy in patients with poor response inhibition. This effect was demonstrated by inducing a better performance on the Stop Signal Task (SST) in pathological gamblers who displayed high levels of self-reported baseline impulsivity (Zack & Poulos, 2009). Similar results have been shown in other drug dependent groups including cocaine and methamphetamine dependent patients, who showed a higher number of negative urine samples (Dackis, Kampman, Lynch, Pettinati, & O'Brien, 2005; Shearer et al., 2009), longer period of abstinence (Anderson et al., 2009), a reduction in substance use (Hart et al., 2006) and less craving (Anderson et al., 2009; Dackis, Kampman, Lynch, Pettinati, & O'Brien, 2005; Shearer et al., 2009) when placed on modafinil compared to other treatments.

1.2. Atomoxetine

Atomoxetine is a selective norepinephrine reuptake inhibitor (SNRI) and is a non-stimulant based drug of choice for the treatment of ADHD (Michelson et al., 2003). Unlike modafinil, due to its mechanism of action, atomoxetine is helpful in patients with depression, especially when ADHD occurs concurrently with depression (Spencer et al., 2006).

In a study by Spencer et al. (2006), 22 adults with ADHD were entered in a double-blind randomized control trial (RCT) with one treatment arm receiving atomoxetine (Spencer et al., 2006). A number of neuropsychological tests were administered to patients in this trail including the Stroop test (testing domains of inhibition), auditory continuous performance (to test sustained attention), Wisconsin Card Sort (To test attentional set shifting), and the Rey–Osterrieth Complex Figures (used to test visual memory). Significant improvements in the Stroop Test alone were detected following three weeks of treatment with atomoxetine, which the authors suggested was indicative of improvements in inhibitory capacity. Despite promising results by Spencer et al., comparatively very few studies have reported the effects of a single dose of atomoxetine on inhibitory control. Chamberlain et al. (2007) reported improved response inhibition on the Stop Signal Task (SST) following a single dose of atomoxetine (60 mg), compared to the administration of placebo or another Selective serotonin re-uptake inhibitor (SSRI), citalopram, in healthy male volunteers (Chamberlain et al., 2007).

In addition to reports of improving inhibitory control, atomoxetine was shown to reduce the frequency of binge eating episodes, reduce BMI numbers and reduce scores on the Hunger subscale of the Three Factor Eating Questionnaire in participants with binge eating disorder (BED) (McElroy et al., 2007). In addition to its short-term effects, a prolonged dose of atomoxetine was found to reduce weight in obese women as part of a 10-week RCT (Gadde, Yonish, Wagner, Foust, & Allison, 2006).

This study aimed to examine the effect of either modafinil or atomoxetine on the cognitive performance of the two behavioral tasks in healthy adult volunteers. Both pharmacological agents are thought to have a similar cognitive profile with regard to the Stop Signal Task, but with unique biological mechanisms of action. However their effect on the commonly used Temporal Discounting (TD) Task is unreported and may make a valid contribution to the literature. Furthermore, the findings can add to obesity research and interventions as eating behaviors are to a large extent shaped by experience and the cognitive processes involved in regulating food intake such as reward-based learning (Petrovich, Holland, & Gallagher, 2005). Other factors involved include top-down control over such learned responses in the service of more abstract goals, such as to maintain a healthy weight (Hare, Camerer, & Rangel, 2009).

2. Method

2.1. Subjects and procedures

Forty healthy young male adult volunteers taking no regular medication were recruited by advertisement. The participants were of mean age 23.8 ± 2.3 (range 19–32). Exclusion criteria included any psychiatric illness; visual, auditory or motor impairment; cardiac or neurological illness; a score greater than ten on the Epworth Sleepiness Scale (Johns, 1991); those who answered "yes" to more than two questions on the CAGE (An acronym for the following questions it comprises: Cut down, Annoyed, Guilty about drinking, Eye-opener) questionnaire (Ewing, 1984); a history of drug or alcohol addiction; or consumption of more than eight cups of coffee per day. All participants were advised to stay free from caffeine and alcohol for at least 12 h before commencing the experiment. The study had approval from the study author's institutional ethics committee and all participants gave informed consent before testing.

A double blind randomized controlled trial was used with 40 participants randomized to receive either a single oral dose of a lactose placebo or one of the test substances (200 mg modafinil or 60 mg atomoxetine). A total of 80 test subjects were used within this study. ($n = 20$ receiving the placebo and $n = 20$ receiving modafinil and $n = 20$ receiving atomoxetine). A within-subject study was avoided in order to eliminate any potential learning bias. Participants were recruited in advance to testing and provided with information about the study and possible side effects of the test drugs. The patient family doctor was also informed at the time the patients wish to participate in the study. This allowed two weeks for the family practitioner to voice any concerns, especially with regard to drug interactions with existing medication or to flag up any neurological conditions we were unaware of. On the day of testing it was confirmed whether the participants prior to the study had consumed any stimulants verbally and the test drug was consumed and questionnaires completed in a quiet room. Participants were then monitored and tested three hours after administration of the drug to take into account both their peak plasma concentration.

2.2. Physiological measures

Subjects were invited to attend the study centre on two separate occasions at least seven days apart. A health questionnaire was completed on the first visit. This allowed them a chance to consider their participation into the study. Additional all patients' GPs were informed of their participation in the study. On the second visit, participants completed the CAGE questionnaire, the Barratt's Impulsivity Index (Patton, Stanford, & Barratt, 1995), Cloninger's Temperament and Character Inventory (TCI) (Cloninger, Svrakic, & Przybeck, 1993) and the National Adult Reading Test (NART) (The National Adult Reading Test (NART): Test Manual, 1982). The blood pressure and pulse were taken whilst completing the questionnaires and repeated at 12-minute intervals through out the experiment and at the end of the testing. Finally, the administration of the drug or placebo was given at this visit.