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Impaired facilitation of self-control cognition by glucose in patients with schizophrenia: A randomized controlled study

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ABSTRACT

Objective: Studies in healthy individuals show that exerting self-control consumes cognitive resources, which reduces subsequent self-control performance. Restoring the availability of blood glucose eliminates this impairment. Patients with schizophrenia are found to have self-regulatory dysfunctions. This study aims to investigate whether patient's (a) glucose facilitation effects will be impaired, and (b) will have exaggerated depletion in a self-control task.
Method: 40 patients with schizophrenia-spectrum disorders and 40 normal controls were recruited. A two drinks (glucose vs. placebo) × two depleting phases (self-control depleted vs. non-depleted) between-groups design was used. We examined the blood glucose levels before and after the selfcontrol depletion phase and the subsequent performances in two self-control tasks (handgrip and Stroop tests) after the drink condition.
Results: The four groups (depleting × glucose, depleting × placebo, non-depleting × glucose and nondepleting × placebo) of both patients and normal controls were comparable on a number of characteristics. The change in blood glucose level in the depleting group was significantly different from those in the non-depleting group. Two × two between-subjects ANOVAs were carried out to test the performances in the handgrip and Stroop tasks. Significant interactions were found in healthy controls regarding both tasks. However, a significant interaction was only found in patients regarding the handgrip task but not the Stroop task.
Conclusions: This study demonstrated an abnormal glucose facilitation effect in patients during a cognitive self-control task but not during a physical self-control task. The findings also suggested for the first time that a self-control depletion effect is intact in patients with schizophrenia.

1. Introduction

Patients with schizophrenia often display a range of behavioral abnormalities that suggest failure to inhibit inappropriate responses. This failure may be associated with increased suicidality, aggression and poorer self-regulation in daily activities (Hoptman et al., 2002; Knolle-Veentjer et al., 2008; Kumari et al., 2009; Nolan et al., 2011). Among a range of cognitive impairments, schizophrenia patients perform poorly on cognitive tasks requiring impulse control, which contributes to these negative outcomes. Unfortunately, the understanding of self-control capacity remains limited (Nolan et al., 2011).

Self-control refers to the capacity to restrain or override impulsive and automatic responses that influence goal-directed behaviors (Barkley, 1997). It is a conscious and effortful form of self-regulation that helps to control or modulate thoughts, emotions, desires and behaviors (Gailliot et al., 2007). By exerting self-control, individuals can resist urges to engage in maladaptive behaviors. This is essential for optimal individual and collective functioning (Gailliot and Baumeister, 2007b; Gailliot et al., 2007). In previous studies on healthy subjects, self-control is observed to rely on a limited resource, such that engaging in an act of self-control will deplete some of a "resource pool", leading to a lowering of subsequent self-control capacity (Baumeister et al., 1998; Muraven et al., 1998; Muraven and Baumeister, 2000).

Glucose is proposed to be a mediator for the mechanism of depletion in self-control (Gailliot and Baumeister, 2007a). Glucose is a primary fuel for the brain. Although the brain constitutes only 2% of human body weight, it consumes nearly 20% of its energy (Dunbar, 2009). Fluctuation in glucose levels and availability affects different mental

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activities and cognitive processes (Siesjo, 1978; Weiss, 1986; Newcomer et al., 1999; Stone et al., 2003; Stone and Seidman, 2008). Effortful processes involving executive function are regarded as particularly susceptible to glucose alterations (Benton, 1990; Benton and Owens, 1993), as these controlled processes may use up more glucose than automatic processes, resulting in a lower glucose level (Fairclough and Houston, 2004). Indeed, glucose depletion (lower glucose level) has been associated with criminal behaviors, aggression, impulsivity and decrements in concentration, attention, memory and emotion regulation (Lustman et al., 1991; Benton and Owens, 1993; Donohoe and Benton, 1999; Stone and Seidman, 2008). Restoring the availability of glucose to optimal levels (increase in glucose levels) should replenish self-control ability. The "glucose facilitation effect" has been reported in many studies in healthy humans, for instance, emotion regulation (Gailliot and Baumeister, 2007a), resisting temptations (Shmueli and Prochaska, 2009), stress coping (Simpson et al., 1974), impulse control (Gailliot and Baumeister, 2007a) and prosocial behaviors (Dewall et al., 2008).

One of the most prominent characteristics of schizophrenia is a deficit in executive function, including processes that are currently defined as self-control behaviors. This is manifested by distractibility, inappropriate behaviors, interference incognition, impulse control problems etc. (Cohen et al., 1999). Therefore, the self-control deficits have an important impact on patients' everyday life competence and general functioning. However, studies on executive function seldom address potential factors such as a depletable limited resource pool and the possibility of glucose facilitation. These factors therefore contribute to understanding the nature and extent of cognitive dysfunction in schizophrenia with potential therapeutic implications. Despite substantial evidence for self-control depletion and glucose facilitation effects in healthy populations, however, to our knowledge, these have not been studied in patients with schizophrenia. Needless to say, regulation of the self-control balance can have a significant impact on functioning for schizophrenia patients. We hypothesized that patients (a) will have a blunted response to glucose facilitation. Due to higher prevalence of insulin resistance and impaired glucose tolerance (Ryan et al., 2003; Cohn et al., 2006; Dasgupta et al., 2010), glucose transport and absorption in the brain may be impaired during high cognitive demand in schizophrenia (Duelli and Kuschinsky, 2001; Jansson, 2007; Grillo et al., 2009). This may lead to a diminished response to glucose facilitation such that patients' self-control task performance will not be improved as much as healthy controls after glucose administration. Furthermore, we also hypothesized that patients (b) will have exaggerated depletion in self-control tasks as more resources will be used up due to cognitive deficits.

2. Materials and methods

The protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. All participants provided written informed consent prior to any research activity. This study is registered with the Clinical Trials.gov Identifier: NCT01563016.

2.1. Participants

Forty patients and 40 healthy controls were recruited. The groups were matched for age, gender and education levels. Patients were recruited from outpatient psychiatric units of the Hong Kong West Cluster after being screened by the case clinicians to see if they met the inclusion criteria: (a) they were diagnosed with DSM-IV schizophrenia, schizoaffective disorder, schizophreniform psychosis, brief psychosis, psychosis NOS or delusional disorder; (b) they were ages 15 and above; and (c) they were Cantonese-speaking Chinese. Those with significant neurologic conditions, substance use disorders, intellectual disabilities, allergies to sugar or artificial sweeteners, diabetes mellitus or diabetes-related problems were excluded. Only patients who were judged by their case medical officers to be mentally stable and to fulfill the inclusion criteria were invited to participate. Healthy controls, who did not meet criteria for current Axis I disorders and did not have family histories of schizophrenia-spectrum disorders, were recruited in the community. Similarly, those with significant neurologic conditions, substance use disorders, intellectual disabilities, allergies to sugar or artificial sweeteners, diabetes mellitus or diabetes-related problems were also excluded.

In the current sample, most patients (75%) had Schizophrenia, 10% had Brief Psychotic Disorder, 7.5% had Psychosis NOS, 5% had Schizoaffective Disorder and 2.5% of the cohort had Delusional Disorder. All participants received treatment with either first ($n = 5$) or second generation antipsychotic medications ($n = 33$) (2 data missing), and they all received complete descriptions of the study and provided written informed consents. For participants aged between 15 and 18 years old, both the participants and their parents or guardians provided informed consent.

2.2. Study design

The study utilized a randomized, double-blind, placebo-controlled design. Participants in both the patient and healthy control groups were randomized among four conditions: (a) depletion & glucose, (b) depletion & placebo, (c) non-depletion & glucose and (d) non-depletion & placebo. The randomization code is computer generated for restricted randomization with balance points defined through blocks, which have the allocation ratio 1:1:1:1. Participants in all conditions received standardized instructions throughout the study.

2.3. Procedure

Participants were instructed to have a 3-hour fasting period prior the study. This helped to reduce extraneous variance in glucose measurement. A flow chart of the study procedures is presented in Fig. 1.

2.3.1. Depletion

Participants were tested individually. First, the baseline blood glucose levels were measured. Single-use blood sampling lancets were used for taking blood samples. Blood glucose levels (mmol/l) were measured using an Accu-Chek compact plus meter (Gailliot et al., 2007). Next, participants were asked to complete a letter deletion task (modified from Baumeister et al., 1998). In the first part of the task, all participants were required to cross out all instances of the letters C and F in a passage. Participants were assumed to learn this quickly and become habituated to scanning for every single C and F and crossing them out. Afterwards, participants in the more-demanding condition were instructed to cross out the letter C and F only if there was another vowel (i.e. a, e, i, o, and u) adjacent to the letter in the second passage. Participants in the less-demanding condition were instructed to simply cross out the letters C and F in the second passage. The decrease in performance was calculated from Time performance in the second passage $- 2 \times$ Time performance in the first passage. After completing this task, blood glucose levels were measured a second time.

2.3.2. Facilitation

Next, all participants were randomly administered either glucose (glucose condition) or an artificial sweetener (placebo condition). The glucose beverage contained approximately 160 kcal (44 g), whereas the placebo contained 0 kcal (both were 250 ml (8.5 oz)). Participants and the experimenter were blind to the drinks. As in previous studies (Gailliot et al., 2007), participants rated their taste preference regarding the beverage (i.e. "How pleasant was it for you while drinking the beverage?"), and their current mood and arousal using the Brief Mood Introspection Scale (Mayer and Gaschke, 1988). As glucose is absorbed