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Effects of caffeine intake and smoking on neurocognition in schizophrenia

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ABSTRACT

Although most studies support the beneficial effects of caffeine on neurocognition, its effects have never been assessed in psychiatric patients. In addition, results from studies in smokers are contradictory. Moreover, there are no data available about the neurocognitive effects of caffeine and tobacco together. We explored the concomitant effects of regular caffeine and tobacco intake on neurocognition in 52 schizophrenic patients and 61 healthy controls. Verbal fluency, processing speed, and working, visual and verbal memory were assessed. For each measurement, two tasks with two levels of complexity were administered. Our results showed that caffeine intake had beneficial effects on male schizophrenic patients only in complex tasks requiring deeper cognitive processing (semantic fluency, cognitive speed, working memory, and visual memory). Female patients and controls were unaffected. In contrast, smoking had a negative effect on male, but not on female, schizophrenic patients in semantic fluency. The effects of smoking in controls were inconsistent. In conclusion, our data showed, for the first time, beneficial effects of caffeine intake on neurocognition in male schizophrenic patients. These data suggest that further research of therapeutics based on caffeine is needed, as this could be beneficial for schizophrenic patients. In contrast, smoking appears to be detrimental.

1. Introduction

Caffeine and tobacco are among the most commonly consumed substances in the world. Moreover, it is well established that caffeine intake and smoking in schizophrenia is much more frequent than in the general population (Strassnig et al., 2006; Winterer, 2010). It is known that caffeine intake can be useful to reduce the cognitive decline after sleep deprivation (Snel and Lorist, 2011) and it also seems to protect against cognitive decline (Santos et al., 2010). In contrast to caffeine intake, most studies point to negative effects of smoking on global cognition and the hastened cognitive deterioration of current smokers over the years (Peters et al., 2008), as well as an increased risk of suffering from dementia (Peters et al., 2008).

Some studies have tried to find whether there is a relationship between caffeine intake and performance in some specific cognitive functions. All of them have used healthy participants, and there are no data available for psychiatric patients. In addition, most of them are focused on the acute effects of caffeine administration rather than the effects of regular consumption. Visual memory (Borota et al., 2014) and cognitive speed, measured with the Digit Symbol Substitution Test (DSST) (Mackay et al., 2002), were improved by acute administration of caffeine. When measuring working memory, Smillie and Gökçen (2010) found that only extrovert participants benefited from the administration of caffeine while performing a complex 3-back task, while those performing simpler tasks (1-back or 2-back) or introvert participants did not. In this sense, positive correlation has also been reported between acute administration of caffeine and performance in complex working memory tasks only in extrovert (Smith, 2013) and impulsive (Smith, 2002) participants, while the non-impulsive were impaired by caffeine (Smith, 2002). Some studies found a positive correlation between regular caffeine intake and semantic verbal fluency, in an animal naming task, with female participants (Vercambre et al., 2013). In contrast, Klaassen et al. (2013), using the Sternberg task, found impaired performance produced by administration of caffeine when the task requirements were higher. Others have failed to find any correlation between regular caffeine consumption and performance in the DSST or the Auditory Verbal Learning Test (Kyle et al., 2010).

Studies with healthy participants do not permit the drawing of a clear conclusion about the effects of smoking. Most studies have failed to find an effect, either positive or negative, of regular

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smoking on verbal fluency in middle-aged and young adults (Wagner et al., 2013). Regarding working memory, it seems to be clear that regular smoking does not affect performance in simple tasks such as forward digit span, which requires only a small cognitive load (Wagner et al., 2013). Using more complex tasks which require a higher cognitive load, no differences were found in the letter-number sequencing task (Wagner et al., 2013). Nevertheless, other researchers have shown that smokers performed worse than non-smokers in the DSST (Starr et al., 2007; Wagner et al., 2013) and in the Auditory Verbal Learning Test (Wagner et al., 2013). In contrast, only a few studies have reported benefits from regular smoking. For example, Sabia et al. (2008) found that middle-aged former smokers performed better than never smokers in both semantic and phonemic fluency, although they did not find differences between current smokers and never smokers.

In contrast to the data gathered with healthy participants, smoking seems to improve cognition to some extent in schizophrenia. Some studies with schizophrenic patients have found better performance in processing speed, assessed with the Stroop task, by regular smokers compared to never smokers (Wing et al., 2011), and by patients who were administered nicotine (Barr et al., 2008). Regular smoking (Morisano et al., 2013) and acute nicotine administration (Smith et al., 2002) were also associated to enhanced verbal memory. Jacobsen et al. (2004), applying a nicotine patch 6 h before a working memory assessment, found that high levels of nicotine were associated with a performance improvement in schizophrenic patients only in the 2-back dichotic condition, the most complex of their study, while smoking controls worsened their performance under the same conditions. Similarly, AhnAllen et al. (2008) found reduced reaction time in schizophrenic patients, but not in controls, after the administration of a nicotine patch during 3 h. Furthermore, smoking seems to improve visuospatial working memory (Sacco et al., 2005), selective attention (Hahn et al., 2012), and divided attention (Ahlers et al., 2014). On the other hand, schizophrenic regular smokers performed worse than schizophrenic non-smokers on visuospatial and immediate memory measures, according to Zhang et al. (2012). Iasevoli et al. (2013) failed to find any effect of regular smoking on cognitive speed using the symbol coding task, equivalent to the DSST, and they even found a trend towards worsened performance in the digit sequencing task and the category instances task, which measure working memory and semantic fluency, respectively (Iasevoli et al., 2013). Other studies evaluating the effects of acute nicotine administration did not find differences between nicotine or placebo administration on semantic fluency (Harris et al., 2004), and the letter-number task, measuring working memory (Barr et al., 2008). In studies comparing regular smokers and non-smokers, no differences were found in the TMT task, measuring processing speed (Morisano et al., 2013), and semantic fluency (Zhang et al., 2012).

The general impression that smoking improves cognition in schizophrenic patients, added to further evidence of nicotine reducing negative symptomatology (Smith et al., 2002), supports the self-medication hypothesis of smoking in schizophrenia, which postulates that patients may smoke to experience these positive effects, and is a potential explanation of the high prevalence of smoking in schizophrenia (Ahlers et al., 2014; Hahn et al., 2012; Smith et al., 2002; Winterer, 2010).

It has been proposed that some of the positive cognitive effects of smoking in schizophrenic patients may be mediated by D_1 receptors in the prefrontal cortex (Ahlers et al., 2014; Hahn et al., 2012). Dopaminergic effects on D_1 in the prefrontal cortex have been shown to follow an inverted-U shape (Vijayraghavan et al., 2007), in which the top of the inverted-U would represent the optimal D_1 receptor activation, which would be associated with better cognitive performance. Schizophrenic patients are thought to be in the non-optimal ascending left part of the inverted-U, and would be able to reach the top of the curve by means of tobacco consumption, which can stimulate dopamine release in the prefrontal cortex (Imperato et al., 1986). This could also account for the differential cognitive effects of smoking observed between schizophrenic patients and healthy controls, as the latter may be already located around the top of the curve and the release of dopamine by tobacco consumption would shift healthy controls to the non-optimal descending right part of the curve (Ahlers et al., 2014; Hahn et al., 2012).

Some gender differences have been found regarding caffeine intake and smoking. Male schizophrenic patients smoke (Kim et al., 2013) and, among smokers, also consume more caffeine (Kim et al., 2013) than female schizophrenic patients. Benowitz et al. (2006) reported an accelerated metabolism of nicotine in women compared to men, probably because of the influence of estrogens over the CYP2A6 enzyme, the main responsible of nicotine metabolism. Botella and Parra (2003) found an increase in state anxiety in men, but not in women, after consuming caffeine. Moreover, caffeine seems to have a greater effect on men in reducing somnolence and inducing activation (Adan et al., 2008), suggesting that women are less sensitive to caffeine (Botella and Parra, 2003). With respect to metabolic issues, females are more affected by caffeine than males using the same doses, likely because of their reduced body weight and height (Carrillo and Benitez, 1996).

Currently available data about the effects of caffeine intake and smoking on neurocognition are not clear and are sometimes contradictory. Moreover, most studies are focused on one substance only and few have examined the effects of caffeine intake and smoking together (see for example: Tanda and Goldberg, 2000; Powers et al., 2008), so the concomitant effects are generally not taken into account. This is especially relevant in schizophrenia studies, as most schizophrenic patients consume these substances simultaneously and do so more frequently than the general population. Another weakness of most studies is not taking into consideration the task difficulty; given that simple and complex tasks require different depth of processing (Craik and Tulving, 1975) that may change the cognitive load and may even involve distinct functional brain areas, caffeine intake and smoking may have differential effects depending on the task being performed. Therefore, our aim in this study was to explore the concomitant effects of regular caffeine intake and smoking on some neurocognitive functions, both in schizophrenic patients and controls, employing tasks with two levels of difficulty. Also, we explored gender differences within each group. Although the effects of caffeine on neurocognition have not been studied in the psychiatric population, we expected it to improve performance in both schizophrenic patients and controls, especially in those tasks requiring deeper cognitive processing. Furthermore, given the inconsistent data available about smoking, we sought to explore its effects on schizophrenic patients and controls.

2. Methods

2.1. Participants

A total of 113 participants, 52 patients with schizophrenia, who were admitted to a large hospitalization unit of Parc Sanitari Sant Joan de Déu, and 61 healthy controls, were included in this study, which is part of a broader project.

Inclusion criteria for patients were having schizophrenia (diagnosed according to DSM-IV-TR criteria), age between 18 and 65 years old and fluency in Spanish language. Exclusion criteria were

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