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Effect of GHB-use and GHB-induced comas on dorsolateral prefrontal cortex functioning in humans

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ABSTRACT

Background: Gamma-hydroxybutyric acid (GHB) is a recreational drug associated with increasing numbers of GHB-dependent patients and emergency attendances often related to GHB-induced comas. Working memory (WM) deficits have been reported in association with GHB use, and animal studies have shown that GHB induces oxidative stress in vulnerable WM-related brain areas such as the dorsolateral prefrontal cortex (DLPFC). However, the effects of chronic GHB use and multiple GHB-induced comas on WM-related brain function in humans remains unknown.

Methods: We recruited 27 GHB users with ≥4 GHB-induced comas (GHB-Coma), 27 GHB users who never experienced GHB-induced coma (GHB-NoComa), and 27 polydrug users who never used GHB (No-GHB). Participants performed an n-back WM task during functional magnetic resonance imaging (fMRI) to probe DLPFC functioning.

Results: The GHB-Coma group had lower premorbid IQ (p = .006) than the GHB-NoComa group despite comparable age and education level. There were also group differences in the use of other drugs than GHB. Therefore, all group comparisons were adjusted for IQ and drug use other than GHB. Compared with the GHB-NoComa and the No-GHB groups, the GHB-Coma group showed increased activity in the right DLPFC (p_{SVC} = 0.028) and increased functional connectivity of the right DLPFC with a cluster comprising the left anterior cingulate and medial frontal gyrus (p_{FWE} = 0.003). No significant fMRI differences were observed between the GHB-NoComa and No-GHB groups. Due to technical problems, no behavioural data were collected.

Discussion: These results suggest that multiple GHB-induced comas, but not GHB-use per se, are associated with alterations in WM-related brain function. Public awareness campaigns are required to minimize the potential adverse effects induced by GHB recreational use, and especially GHB-induced comas, even if no immediate side effects are experienced.

1. Introduction

Gamma hydroxybutyric acid (GHB) is a recreational drug that poses a substantial risk for public health (World Health Organization, 2015). A recent increase in the number of individuals seeking treatment for GHB dependence and emergency room attendances often related to GHB-induced comas, are just some of the indicators of the potential public health risks associated with recreational GHB use (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2016; Public Health England, 2015; United Nations Office on Drugs and Crime, 2017). However, despite a disproportional number of severe side effects, GHB remains popular amongst party goers due its effects of euphoria, loss of inhibition, and sexual arousal (Abanades et al., 2006; European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2016; Korf et al., 2014; Miró et al., 2017; Public Health England, 2015; United Nations Office on Drugs and Crime, 2017; Van Amsterdam et al., 2012).

Neverthless, recreational use of GHB poses a high risk of intoxication with severe side effects, resulting from a narrow dose-response window between the desired high and overdose (Abanades et al., 2006; Korf et al., 2014; Miró et al., 2017; Van Amsterdam et al., 2012). Amongst these severe adverse effects GHB-induced coma is one of the most common, lasting between 1 and 4 h and frequently reaching the most critical classification on the Glasgow Coma Scale (Abanades et al.,

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2006; Korf et al., 2014; Miró et al., 2017; Van Amsterdam et al., 2012). Remarkably, GHB users awake from these comas with no apparent negative outcomes, leading them to believe that GHB use is safe and GHB-induced comas are innocent events (Korf et al., 2014; Van Amsterdam et al., 2012).

However, upon its discovery GHB was widely used as a general anaesthetic, being GHB-induced comas compared to a state of pharmacological-induced unconsciousness (Miró et al., 2017; Van Amsterdam et al., 2012). Research on pharmacological induced unconsciousness (anaesthesia) in humans suggest that without oxygen support, even if transient, these states may induce neural deprivation of oxygen (hypoxia) and consequently lead to oxidative stress in vulnerable regions related to the WM-network such as the dorsolateral prefrontal cortex (DLPFC) (Perouansky and Hemmings, 2009). DLPFC is a region particularly rich in GHB-bindings sites and animal studies show this region to be highly vulnerable to GHB-induced neurotoxic effects (Castelli et al., 2000; Johansson et al., 2014; Pedraza et al., 2009). In line with these findings, impairments in cognitive processes such as WM have been associated with GHB administration in animals, but similar impairments have also been reported in humans who regularly used GHB (Abanades et al., 2006; Carter et al., 2009a, 2009b; Johansson et al., 2014; Korf et al., 2014; Pedraza et al., 2009).

Neuroimaging research on the effects of GHB in humans is still on its early days with studies only assessing the acute effects of GHB on brain functioning. These studies suggest that acute administration of GHB induces alterations in activity and connectivity of regions of the PFC and the limbic system that are associated with alterations in emotional awareness and prosexual behaviour (Bosch et al., 2017a, 2017b). However, little is known about the neural effects of regular recreational use of GHB and GHB-induced comas on the human brain. In order to investigate the effect of GHB-use and GHB-induced comas on WM related brain function, we used functional magnetic resonance imaging (fMRI) (Owen et al., 2005). The dorsolateral part of the PFC (DLPFC) is the integrative hub of the WM network (D'Esposito and Postle, 2015; Owen et al., 2005). This region is responsible for the storage of task-relevant sensory information, but also for integrating this incoming information into top-down goal-directed behaviour (D'Esposito and Postle, 2015; Niendam et al., 2012; Ranganath and D'Esposito, 2001; Rissman et al., 2008). Interestingly, altered activity and functional connectivity of the DLPFC is regularly seen in alcohol use disorder, another well-known GABA-substance use disorder (Campanella et al., 2013; Desmond et al., 2003; Han et al., 2015; Wilcox et al., 2014).

Based on the WM impairments associated with GHB administration in animals and humans, we expect that regular GHB use will particularly affect DLPFC neural processing during a WM functional magnetic ressonance imaging (fMRI) task. To disentangle the effects induced by GHB use itself from the effects induced by multiple GHB-induced comas, we recruited three groups of participants: (1) GHB users who had ≥4 GHB-induced comas, (2) GHB users who never had a GHB-induced coma, and (3) polydrug users who never used GHB. This allowed us to assess: (a) the GHB-induced coma effect by comparing GHB users who had multiple GHB-induced comas with GHB users who never had a GHB-induced coma and polydrug users who never used GHB; and (b) the effect of GHB use per se by contrasting GHB users who never had a GHB-induced coma with polydrug users who never used GHB.

2. Materials and methods

2.1. Participants

In this cross-sectional study, 81 male participants were recruited trough addiction centers in the Netherlands, flyers, internet advertisement and snowball sampling. To be included in the study, all participants had to be native Dutch speakers, between 18 and 40 years old. We only recruited males as the vast majority of GHB users are men (Miró et al., 2017). We recruited three distinct groups of participants, matched for age and educational level: 27 GHB users who had at least ≥4 GHB-induced comas (GHB-Coma); 27 GHB users without a history of GHB-induced coma (GHB-NoComa); 27 polydrug users who never used GHB (No-GHB). To be included in the GHB groups participants had to use GHB ≥ 25 times in the 2 years preceding the assessment (De Jong and Dijkstra, 2013). The threshold of 4 comas for inclusion in the GHB-Coma group was selected to maximize potential differences with the GHB-NoComa group. Polydrug use comprised the use of alcohol, nicotine, cannabis, cocaine, stimulants other than cocaine, ecstasy, ketamine, and sedatives other than GHB. MRI data from 3 GHB-Coma participants, 2 GHB-NoComa participants, and 1 No-GHB participant had to be discarded due to excessive head movement inside the scanner and/or insufficient brain coverage.

Potential participants were excluded if they had a history of epilepsy; if underwent general anaesthesia on the 2 years preceding the study; if any contra-indication was reported for fMRI scanning (e.g. metal object in the body); if any coma episode not related to GHB use was reported; or if they were currently under treatment for narcolepsy with cataplexy (since treatment involves the use of Xyrem, brand name for GHB) (Abanades et al., 2006; Carter et al., 2009a, 2009b). After an explanation of the study, written informed consent was obtained from all the participants prior to the study initiation. This study was in accordance with the Helsinki Declaration principles (7th revision, 2013), the Medical Research Involving Human Subjects (World Medical Association, 2013), and approved by the Medical Ethics Review Committee of the Academic Medical Centre (Büller et al., 2010; World Medical Association, 2013). The data presented here are part of a larger study investigating the effects of recreational GHB use in humans. The study consisted of an initial urine test, followed by completing questionnaires related to GHB and other drug use, depression, anxiety, stress and impulsivity levels. During the subsequent neuroimaging session, structural and functional scans were collected in the following order: structural; resting-state; long-term memory (paired association task); diffusion weighted imaging, WM (the present n-back task); emotion processing (face matching task). Finally outside the scanner, participants performed digitized neuropsychological testing including verbal memory, spatial memory, intra-extra dimensional set shifting and probabilistic reversal learning. The focus of the current manuscript is solely about WM, and data from other experiments will be presented elsewhere (Raposo Pereira et al., 2018).

2.2. Clinical assessment

Drug use was assessed with the substance use section of the MATE 2:1 questionnaire, and premorbid intellectual functioning as proxy for IQ was assessed with the Dutch version of the National Adult Reading test (Schippers et al., 2011; Schmand et al., 1991).

2.3. Statistical analysis

Demographic and clinical data were analyzed with SPSS24 software (IBM Software Analytics, New York, USA). Normally distributed data were assessed with Analysis of variance (ANOVA). When not normally distributed, data were transformed or assessed using non-parametric tests (see Tables 1and 2). Differences between GHB groups were considered in terms of total exposure to GHB as defined by years of use × daily dose, daily dose during last month (ml/day), years since first use, and prevalence of days using GHB in the previous month. Exposure to other drugs, defined as years of weakly use × daily dose, was assessed for alcohol, nicotine, cannabis, cocaine, stimulants other than cocaine, ecstasy, ketamine, and sedatives (Table 2). Neuroimaging analyses were adjusted for group differences in demographic variables, IQ and exposure to drugs other than GHB.