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Quetiapine modulates functional connectivity in brain aggression networks

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ABSTRACT

Aggressive behavior is associated with dysfunctions in an affective regulation network encompassing amygdala and prefrontal areas such as orbitofrontal (OFC), anterior cingulate (ACC), and dorsolateral prefrontal cortex (DLPFC). In particular, prefrontal regions have been postulated to control amygdala activity by inhibitory projections, and this process may be disrupted in aggressive individuals. The atypical antipsychotic quetiapine successfully attenuates aggressive behavior in various disorders; the underlying neural processes, however, are unknown. A strengthened functional coupling in the prefrontal–amygdala system may account for these anti-aggressive effects. An inhibition of this network has been reported for virtual aggression in violent video games as well. However, there have been so far no in-vivo observations of pharmacological influences on corticolimbic projections during human aggressive behavior. In a double-blind, placebo-controlled study, quetiapine and placebo were administered for three successive days prior to an fMRI experiment. In this experiment, functional brain connectivity was assessed during virtual aggressive behavior in a violent video game and an aggression-free control task in a non-violent modification. Quetiapine increased the functional connectivity of ACC and DLPFC with the amygdala during virtual aggression, whereas OFC–amygdala coupling was attenuated. These effects were observed neither for placebo nor for the non-violent control. These results demonstrate for the first time a pharmacological modification of aggression-related human brain networks in a naturalistic setting. The violence-specific modulation of prefrontal–amygdala networks appears to control aggressive behavior and provides a neurobiological model for the anti-aggressive effects of quetiapine.

Introduction

Aggressive behavior (AB) constitutes a major burden to society. It complicates the course of various psychiatric disorders (Arseneault et al., 2000) and is associated with worse treatment response and poor prognosis (Hoptman and Antonius, 2011; Volavka, 2002). AB has been linked to positive psychotic symptoms, and the administration of atypical antipsychotics such as quetiapine has been suggested (Arango and Bernardo, 2005). Quetiapine, which is characterized by both serotonergic and dopaminergic properties, is effective also in the treatment of AB in antisocial personality disorder (Walker et al., 2003), borderline personality disorder (Perrella et al., 2007), and bipolar disorder (Buckley et al., 2007). A recent review on the efficacy of quetiapine in the treatment of aggression showed a significant attenuation of AB in 8 out of 9 investigated studies, suggesting that the drug may be suitable for treatment of various forms of AB (Comai et al., 2012b). However, the symptom specificity and the underlying neural mechanisms are unknown.

From a neurobiological perspective, AB in overly aggressive individuals has been associated with a dysfunctional circuit encompassing the amygdala and prefrontal cortex areas, in particular the anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), and dorsolateral prefrontal cortex (Bufkin and Luttrell, 2005; Davidson et al., 2000; Markowitsch and Staniloiu, 2011; Passamonti et al., 2008; Siever, 2008). These areas constitute a neural system involved in affective control and stress regulation (Lederbogen et al., 2011). Current models postulate that prefrontal cortex areas exert a top-down inhibitory control over the amygdala; this effect has been associated with successful affective regulation and suppression of aggressive impulses (Bufkin and Luttrell, 2005). This neural system may be structurally and functionally impaired in aggressive individuals (Birbaumer et al., 2005; Matsuo et

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al., 2009; Schneider et al., 2000; Siever, 2008; Yang and Raine, 2009). Dysfunctions in prefrontal amygdala regulation have been assigned to altered transmission of serotonin (5-hydroxytryptamine, 5-HT). Reduced levels of the main serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid are consistently associated with elevated AB (Comai et al., 2012a). Similarly, a reduction of 5-HT via acute tryptophan depletion has been shown to induce AB in behavioral tasks fostering aggression (Bjork et al., 1999). Habitually elevated 5-HT levels, in turn, show a similar effect. Excessive 5-HT due to monoamine oxidase A (MAOA) gene mutations (Brunner et al., 1993) or low-expressing MAOA gene alleles (Buckholtz and Meyer-Lindenberg, 2008) promotes a disturbed orbito-mediofrontal-amygdala circuit and has been associated with trait aggression (Alia-Klein et al., 2008) and susceptibility to adverse life events (Caspi et al., 2002; Kim-Cohen et al., 2006). Being a serotonergic drug with both 5-HT 2A antagonistic and 5-HT 1A agonistic effects, quetiapine may thus attenuate AB by modulating functional connectivity in the orbito-mediofrontal-amygdala system.

However, functional imaging studies of aggression are rare since overt AB is difficult to experimentally induce. A feasible and valid model is virtual reality which permits AB against virtual characters without negative consequences for real persons and has been successfully employed in neuroimaging experiments (Cheetham et al., 2009; Klasen et al., 2012; Mathiak et al., 2011). Virtual and real aggression correlate in human populations and AB in video games has been shown to induce short-term aggressive tendencies (Anderson et al., 2010). Furthermore, real and virtual aggression forms share common neural substrates: AB in video games inhibits rostral ACC regions and amygdala, along with activation of the dorsal ACC (dACC) (Mathiak and Weber, 2006; Weber et al., 2006) in line with the suggested neurophysiological circuits underlying real-life AB.

This study addressed the neural substrates of AB as modeled in a violent video game and their modification by quetiapine. In a double-blind placebo-controlled cross-over design, functional magnetic resonance imaging (fMRI) was employed to measure brain activity in thirteen healthy male subjects during unrestrained playing of a violent game (*Carmageddon: TDR 2000*, Torus Games, Bayswater, Australia, 2000) and a non-violent modification without virtual AB (Carnagey and Anderson, 2005). Each subject played violent and control (non-violent) conditions in randomized order once under quetiapine and once under placebo. Based on the serotonergic properties and anti-aggressive effects of quetiapine and on the model of prefrontal amygdala regulation, we hypothesized that quetiapine a) attenuates game-induced aggressive feelings as assessed by self-reports and b) modulates functional connectivity in an aggression network comprising the amygdala and the prefrontal regions ACC, OFC, and DLPFC during virtual AB. Furthermore, we explored c) the relationship between the attenuation of aggressive feelings and the effect sizes of brain connectivity in these areas for the drug–violence interaction. Specifically, a stronger coupling of the network should be paralleled by less game-induced aggressive feelings.

Materials and methods

Participants

Thirteen right-handed male subjects (21–28 years, mean 24.9 ± 2.6) participated in the experiment. All subjects were regular video game players (min. 5 h/week), had normal or corrected to normal vision, normal hearing, no contraindications against MR investigations or quetiapine, no history of neurological or psychiatric illness, and no history of psychopharmacological therapy. Experienced gamers were chosen to minimize potential distracting effects of the virtual environment and to assure good motor skills for game control. Given the popularity of video games in young males (Entertainment Software Association, 2013), the sample may still represent a significant population. The experiment was designed according to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 2008: http://www.wma.net/en/30publications/10policies/b3/17c.pdf); the study protocol was approved by the local Ethics Committee as well as by the Federal Institute for Drugs and Medical Devices (BfArM). After complete description of the study to the subjects, written informed consent was obtained.

Procedure

Before the measurements, quetiapine or placebo was administered over three days in increasing dosage (50, 100, and 300 mg/24 h, respectively). Blood serum levels accordingly confirmed quetiapine intake (156.9 ± 142.5 μg/l). Each subject was measured on two days, i.e. once in the placebo and once in the drug condition, with a washout phase of two weeks between measurements. During four scanning sessions (10 min each), the subjects played the violent video game *Carmageddon: TDR 2000* (Torus Games, Bayswater, Australia, 2000) in unrestricted manner. In this racing game, the player kills pedestrians with his car. The game contains a substantial amount of AB with excessive depiction of blood splatter, accompanied by painful screams of the virtual victims. As a non-violent condition, we introduced a modified version without pedestrians in two of the four sessions. Here, the task was to pick up as many valuable items as possible, i.e. colorful icons such as triangles or rectangles (control events). These icons exploded in sparkles when the player drove over them, suggesting a comparable level of sensory stimulation as in the violent condition. Both the pedestrians and the icons were situated all over the game map, on the main track of the racing game as well as in hidden places such as inside buildings, on rooftops, or in mine tunnels. Therefore, both the violent and the control condition asked for active exploration of the game map as well as for a high level of motor planning and performance. Representative scenes from both conditions, depicting violent and control events, are shown in Fig. 1. Each subject played two violent and two non-violent sessions in randomized order. Visual stimulation and game sound were delivered via MR compatible video goggles and headphones; sound levels were adjusted individually to a comfortable level.

Aggressive feelings were assessed with the State Trait Anger Expression Inventory (STAXI; state version; Spielberger, 1988, German version by Schwenkmezger, Hodapp & Spielberger, 1993). On each of the days, subjects completed the STAXI immediately before and after the game play fMRI measurements. This procedure allowed for an independent assessment of drug effects, game effects, and for the drug × game interaction effects on state anger and aggressive feelings.

Image acquisition

Whole-brain fMRI was conducted with echo-planar imaging (EPI) sequences (TE = 28 ms, TR = 2000 ms, flip angle = 77°, voxel size = 3 × 3 mm, matrix size = 64 × 64, 34 transverse slices, 3 mm slice thickness, 0.75 mm gap) on a 3 Tesla Siemens Trio scanner (Siemens Medical, Erlangen, Germany) with a standard 12-channel head coil. On each of the measurement days, 1240 functional images were acquired in four sessions (310 volumes each). After completing the functional measurements, high-resolution T1-weighted anatomical images were performed using a magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence (TE = 2.52 ms; TR = 1900 ms; flip angle = 9°; FOV = 256 × 256 mm^2; 1 mm isotropic voxels; 176 sagittal slices).

Image analysis

Image analyses were performed with *BrainVoyager QX 2.2.1* (Brain Innovation, Maastricht, The Netherlands). Preprocessing included slice scan time correction, 3D motion correction, Gaussian spatial smoothing (4 mm FWHM), and high-pass filtering including linear trend removal. The first five images of each session were discarded