Progress in Neuro-Psychopharmacology & Biological Psychiatry 45 (2013) 1–6

Contents lists available at SciVerse ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

Brain structural abnormalities in Doberman pinschers with canine compulsive disorder

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ARTICLE INFO

Article history:
Received 15 November 2012
Received in revised form 3 April 2013
Accepted 3 April 2013
Available online 13 April 2013

Keywords:
Blanket and flank sucking
Compulsive disorder
Diffusion tensor imaging
Doberman pinschers
Voxel-based morphometry

ABSTRACT

Obsessive compulsive disorder (OCD) is a debilitating condition, the etiology of which is poorly understood, in part because it often remains undiagnosed/untreated for a decade or more. Characterizing the etiology of compulsive disorders in animal models may facilitate earlier diagnosis and intervention. Doberman pinschers have a high prevalence of an analogous behavioral disorder termed canine compulsive disorder (CCD), which in many cases responds to treatments used for OCD. Thus, studies of CCD may help elucidate the etiology of compulsive disorders. We compared brain structure in Dobermans with CCD (N = 8) and unaffected controls (N = 8) to determine whether CCD is associated with structural abnormalities comparable to those reported in humans with OCD. We obtained 3 Tesla magnetic resonance structural and diffusion images from anesthetized Dobermans and subjected images to segmentation, voxel based morphometry, and diffusion tensor analyses. CCD dogs exhibited higher total brain and gray matter volumes and lower dorsal anterior cingulate cortex and right anterior insula gray matter densities. CCD dogs also had higher fractional anisotropy in the splenium of the corpus callosum, the degree of which correlated with the severity of the behavioral phenotype. Together, these findings suggest that CCD is associated with structural abnormalities paralleling those identified in humans with OCD. Accordingly, the CCD model, which has a number of advantages over other animal models of OCD, may assist in establishing the neuroanatomical basis for and etiology of compulsive disorders, which could lead to earlier diagnosis of and new treatments for humans and animals with these disorders.

1. Introduction

Obsessive compulsive disorder (OCD) is a debilitating condition with a lifetime prevalence of about 2% of the population (Ruscio et al., 2010). According to the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2000), OCD symptoms include obsessions, intrusive recurrent and persistent thoughts, impulses, or images that cause marked anxiety or stress, which are time consuming or significantly interfere with normal routine; symptoms also include compulsions, such as repetitive behaviors or mental acts that the patient feels driven to perform to neutralize the obsession. Cortico-striatal circuitry has been implicated as playing a key role in OCD, but additional brain elements now are thought to contribute to the disorder, including anterior cingulate and orbitofrontal cortices, as well as amygdalo-cortical circuitry (Milad and Rauch, 2012).

OCD typically is not diagnosed until nearly a decade after symptom onset (Stengler et al., 2013), making it difficult to characterize the etiology of the disorder in humans. Accordingly, several rodent models have been developed to study compulsive disorders. These include transgenic and in-bred mouse lines that exhibit several of the hallmarks of OCD such as compulsive behaviors, some of which are ameliorated by serotonergic agents typically used to treat OCD in humans (Greene-Schloesser et al., 2011; Shmelkov et al., 2010; Welch et al., 2007).

Canine models offer several advantages over rodent models in that canine central nervous system genetics (Ostrander and Wayne, 2005) and neuroanatomy are more similar to humans than mice, and the dog brain is many times the size of the mouse brain. Dogs and humans live together and dogs have adapted to human social environments. Moreover, more than 200 canine disorders have close similarities to

Abbreviations: OCD, obsessive compulsive disorder; CCD, canine compulsive disorder; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic anti-depressants; PET, positron emission tomography; NMDA, N-Methyl-D-aspartate; OFC, orbitofrontal cortex; ACC, anterior cingulate cortex; ROI, region of interest; FA, fractional anisotropy; CDH2, cadherin 2 gene; BS, blanket sucking behavior; FS, flank sucking behavior; VWD, Von Willebrand's disease; DTI, diffusion tensor imaging; VBM, voxel based morphometry; CSF, cerebrospinal fluid; ADC, apparent diffusion coefficient.

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http://dx.doi.org/10.1016/j.pnpbp.2013.04.002

human disorders (Parker et al., 2010; Tsai et al., 2007), including the canine analog of OCD, canine compulsive disorder (CCD). CCD derives from normal species-typical behavior, including grooming (acral lick dermatitis), predatory behavior (tail chasing), eating/suckling (pica and flank/blanket sucking) and locomotion (pacing/circling) (Luescher, 2003; Overall and Dunham, 2002; Rapoport et al., 1992; Shuster and Dodman, 1998). CCD is highly prevalent among Dobermans, with an estimated incidence of about 28% in a database including over 2300 dogs (personal communication, Andrew Borgman, Statistical Analyst, Van Andel Research Institute, Grand Rapids, MI). Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine or tricyclic anti-depressants (TCAs) such as clomipramine used to treat human OCD (and as noted above are effective in rodent compulsive disorder models), also are commonly employed to treat CCD (Goldberger and Rapoport, 1991; Hewson et al., 1998; Irimajiri et al., 2009; Moon-Fanelli and Dodman, 1998; Overall, 1994; Stein et al., 1998; Wynchank and Berk, 1998). Further, it has been shown that humans with OCD (Aboujaoude et al., 2009; Feusner et al., 2009; Stewart et al., 2010) and dogs with CCD respond to treatment with the glutamatergic NMDA receptor antagonist memantine (Schneider et al., 2009). In addition, positron emission tomography (PET) imaging detected serotonergic and dopaminergic abnormalities in dogs with CCD, paralleling some reports in humans with OCD (Vermeire et al., 2012). Thus, dogs with CCD respond to treatments that improve OCD symptoms and exhibit behavioral and neurochemical phenotypes similar to those found in OCD, suggesting that the CCD model may be useful for studying the etiology of compulsive disorders.

However, to date, no studies have reported on whether brain structural abnormalities exist in dogs with CCD. Brain regions most consistently found to be abnormal in humans with OCD include the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), insula, thalamus, corpus callosum, and striatum (Song et al., 2011; Zarei et al., 2011). ACC abnormalities include reduced gray matter volumes and densities (Carmona et al., 2007; Gilbert et al., 2008; Matsumoto et al., 2010b; Rotge et al., 2010; Valente et al., 2005; Yoo et al., 2008). Fractional anisotropy abnormalities have been found in the corpus callosum (den Braber et al., 2011; Garibotto et al., 2010; Nakamae et al., 2011; Yoo et al., 2007; Zarei et al., 2011). Together, these findings support the idea that structural abnormalities in multiple brain areas contribute to OCD (Milad and Rauch, 2012). Accordingly, we sought to determine whether Dobermans diagnosed with CCD exhibit brain abnormalities comparable to those found in humans with OCD.

We acquired 3 Tesla structural and diffusion weighted images from anesthetized Dobermans diagnosed with CCD and from a matched sample of behaviorally normal dogs. We analyzed structural images using a whole-brain approach including tissue segmentation and voxel based morphometry. Because our diffusion images were of lower spatial resolution and because they had lower signal to noise ratios than our structural images, we conducted a region of interest (ROI) analysis limited to 3 selected ROIs (genu and splenium of corpus callosum and cingulum bundle). We hypothesized that we would observe higher fractional anisotropy (FA) in these ROIs, which would reflect greater anisotropy of water diffusion between white matter fibers and possibly greater ordering of fiber bundles. Higher FA values in these areas have been reported in humans with OCD (Cannistraro et al., 2007; Yoo et al., 2007; Zarei et al., 2011).

2. Methods

This study was conducted according to national and international guidelines for canine research. Informed consent was obtained from all owners. The study was reviewed and approved by the Clinical Studies Review Committee (CSRC# 090-09) of Tufts Cummings School of Veterinary Medicine. The MRI study components were reviewed and approved by the McLean Hospital Institutional Animal Care and Use Committee (IACUC# 09-8/2-27).

2.1. Subjects

Doberman pinscher dogs included in this study were recruited at local dog shows and via advertisement through the Pilgrim Doberman Pinscher Club and the website of the Animal Behavior Clinic in Tufts Cummings School of Veterinary Medicine (TCSVM). We recruited dogs aged 1.5 to 6 years old, to avoid effects related to brain development or brain aging. Nineteen dogs were recruited, 16 of which (8 dogs with CCD (6 males) and 8 controls (2 males)) were clinically cleared for imaging. Because of the relatively small sample sizes available, it was not possible to match control and CCD groups with respect to sex. Owners of these dogs were required to complete the same detailed behavior assessment questionnaire employed in a prior phenotypic survey of CCD-affected and control Doberman pinschers (Moon-Fanelli et al., 2007) and in a prior study linking a genetic polymorphism in the cadherin 2 (CDH2) gene to CCD (Dodman et al., 2010). In addition, owners were interviewed by veterinary behaviorists affiliated with the Animal Behavior Clinic at TCSVM. When necessary, owners were asked to send videos of their dog's behavior to aid in behavioral phenotyping. Eight dogs were diagnosed as exhibiting either compulsive blanket sucking behavior (BS) or flank sucking behavior (FS). Two out of 8 affected dogs were positive on a DNA test for Von Willebrand's disease (VWD), which causes a deficiency of a platelet clotting factor that can result in increased bleeding. Dobermans are predisposed to develop VWD, the most commonly inherited bleeding disorder of dogs. One affected dog had a history of episodic head tremor, but did not exhibit head tremor at the time of the MRI.

CCD dogs were ranked for the severity of their behavior by determining the numbers of hours the dogs engaged in BS/FS behavior during a typical 24-hour period. When ties emerged, we used the presence of an additional compulsive behavior, such as acral lick dermatitis or pica, as well as disorder duration (the numbers of years dogs exhibited BS/FS before the study), to further inform the rankings. None of the dogs had received any medications or behavior modification treatments designed to modify behavior.

A separate group of 8 Dobermans not exhibiting any CCD behaviors or other behavior problems was enrolled as a control group. Since the dogs enrolled in the study were to be anesthetized for the MRI procedure, a complete physical examination, including echocardiogram examination as well as blood work, including CBC, chemistry profile, total thyroxine (T4), N-terminal pro B-type natriuretic peptide (NT-proBNP; Cardiopet™ proBNP test, IDEXX Laboratories, Inc., Westbrook, ME, USA), were performed on all 16 dogs. Echocardiography, including standard M-mode, 2-dimensional, color-flow, spectral Doppler and tissue Doppler imaging was performed by a board-certified veterinary cardiologist in all dogs (GE Vivid 7™, GE Medical systems, USA). Continuous ECG monitoring was implemented during the echocardiographic examination. No dogs showed any clinical signs of heart disease. Dogs cleared of medical complications that might impact the dog's well being under anesthesia were brought to the McLean Imaging Center at McLean Hospital, Belmont MA for MRI imaging. The MRI images were examined by a board certified veterinary radiologist at TCSVM to identify any gross structural abnormalities that might affect behavior.

2.2. Anesthesia

After fasting for 8 h and withdrawal of water for 2 h, all dogs were premedicated by intravenous injection of acepromazine (0.025 mg/kg) and butorphanol (0.05 mg/kg) and then had anesthesia induced with intravenous propofol (3 mg/kg). Anesthesia was maintained using 2% isoflurane/oxygen mixture delivered via a semi-closed circle absorber anesthetic circuit. Respiratory rates were monitored and pulse oximetry was used to monitor heart rates and oxygen saturations constantly throughout MRI imaging.