Impaired Prepulse Inhibition of Acoustic Startle in Obsessive-Compulsive Disorder

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Background: *Animal and clinical studies suggest that impaired sensorimotor gating, as assessed with the prepulse inhibition (PPI) paradigm, may result from dysfunctional frontostriatal brain circuits and from neurochemical alterations which are also implied in the pathophysiology of obsessive-compulsive disorder (OCD). However, there is only preliminary evidence about impaired PPI in OCD so far.*

Methods: *Acoustic PPI was measured in 30 OCD patients and 30 matched healthy controls with a paradigm using different prepulse intensities. Psychopathology assessment included ratings for obsessions, compulsions, and depression.*

Results: *PPI was reduced in OCD patients, and this deficit was most pronounced for most intense (16 dB(A)) prepulses, where mean PPI was 39.6% in unmedicated patients (n = 4), 45.8% in medicated patients, and 58.9% in controls. No group differences were observed with regard to the habituation of acoustic startle magnitude. Startle measures were generally not associated with clinical measures, although such associations may have been obscured by medication effects.*

Conclusions: *The present study confirms deficient central inhibitory functioning in patients with OCD and supports the model of deficient frontostriatal circuits in OCD. The relationship of PPI deficits to pharmacological and behavioral treatment and to possible subtypes of OCD merits further study.*

Key Words: Obsessive-compulsive disorder, prepulse inhibition, habituation, acoustic startle response, sensorimotor gating, clinical studies

Individuals with obsessive-compulsive disorder (OCD) are characterized by an inability to inhibit both undesired intrusions (thoughts or images) and repetitive stereotypical behavior (e.g., excessive washing or checking). OCD symptoms have been associated with dysfunctions in cortico-striato-pallido-pontine (CSPP) circuits (for a review, see Stein 2002, 2000; Wilson 1998). These circuits are also known to regulate both the startle reflex and the inhibition of this reflex by weak prepulses (Swerdlow et al 2001; Koch 1999).

The startle reflex constitutes a reflexive contraction of the skeletal and facial muscles in response to a sudden, relatively intense stimulus that may be presented across multiple modalities (visual, auditory, or tactile). In human studies, electromyography (EMG) of the orbicularis oculi muscle is typically used to measure the eye-blink component of the acoustically evoked startle reflex. Interest in the startle response has been motivated primarily because of two forms of plasticity that are evident across species: prepulse inhibition (PPI) and habituation.

PPI, first described by Graham (1975), is defined as a reduction of the startle reflex because of a weak sensory prestimulation. Further developments by Braff and colleagues (1978, 1992) have firmly established PPI as an operational measure of (deficient) sensorimotor gating. Sensorimotor gating is a process whereby a sensory event (e.g., acoustic prepulse) suppresses the motor response (e.g., eye blink) to a later stimulus (e.g., acoustic startle stimulus), thus enabling the organism to process relevant information selectively and efficiently.

The neurochemistry and neuroanatomy implied in the pathophysiology of OCD are also important in the mediation of the startle reflex and its inhibition. Converging evidence from functional neuroimaging studies in OCD has implicated dysfunction in a cortic-striato-thalamo-cortical network (Saxena et al 1998), including metabolic hyperactivity primarily within the orbitofrontal cortex and the striatum, which is accentuated during symptom provocation (Rauch et al 1994; Breiter et al 1996) and attenuated following successful treatment (Baxter et al 1992; Schwartz et al 1996; Nakatani et al 2003). Morphometric studies in OCD also reported subtle volumetric abnormalities in the fronto-striatal brain regions (Robinson et al 1995; Rosenberg et al 1997; Pujol et al 2004). These fronto-striatal brain regions, which are found to be impaired in OCD patients, are also important for the mediation of the startle response and its inhibitory control (Swerdlow et al 1995b; Kumari et al 2003).

Modulations of the startle response and PPI-regulating CSPP circuits are brought about by several neurotransmitter systems (Koch 1999), including—among others—serotonin (5-HT) and dopamine, that are also known to be implicated in the pathophysiology of OCD (Stein 2002). Dysfunction of the serotonin system in OCD has been hypothesized primarily because of the anti-obsessional efficacy of selective serotonin reuptake inhibitors (SSRIs; Baumgarten and Grozdanovic 1998). However, serotonin does not have a singular role in OCD (Goodman et al 1992). Preclinical evidence points to important interactions between both systems (Kapur and Remington 1996), and there is increasing evidence for an additional involvement of the dopamine system in OCD: the dopamine system has shown its importance for stereotypical behavior in animal models (Goodman et al 1990). Pharmacologic agents influencing the dopaminergic system (e.g., cocaine, bromocriptine) have been shown to induce obsessive-compulsive symptoms (Jenike et al 1990). Conversely, anti-dopaminergic augmentation was reported to be useful in SSRI monotherapy–refractory OCD patients (McDougle et al 1994, 2000; Bystritsky et al 2004). It is interesting that dopamine agonists were also found to disrupt PPI in rodents, whereas anti-dopaminergic substances were shown to have an antagonizing effect on PPI disruptions both in rats (Geyer et al 2001) and in humans (Kumari et al 1999, 2000; Weike et al 2000; Hamm et al 2001). Furthermore, clinical evidence also includes the observation that infarcts of the basal ganglia, which are intimately linked

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to rich dopaminergic innervations, have been associated with the late-onset emergence of obsessive-compulsive behavior (Carmin et al 2002). Finally, in line with this reasoning for an involvement of the dopaminergic system in the pathophysiology of OCD, Denys et al (2004) have recently provided in vivo evidence for abnormal dopamine function in the caudate nucleus of OCD patients, as indicated by down-regulation of the dopamine D_2 receptor density in this brain region.

The phenomenology of OCD includes obsessive intrusions (the inability to inhibit undesired thoughts or images) and repetitive stereotypical behavior (e.g., excessive washing or checking). The assumption that poor inhibition in OCD, defined at the level of intrusive obsessions and compulsions, might be related to poor inhibition at the level of prepulse-related startle attenuation is intriguing. Such a link might be helpful for further elucidation of the neurocognitive substrate of the disinhibition seen in patients with OCD. Some evidence in favor of such a relationship between physiological and clinical inhibition deficits has been found in a study by Perry and Braff (1994), who demonstrated in schizophrenics a correlation between startle PPI and thought disorder, as assessed by the "suppression" failures on the Ego Impairment Index. However, another attempt to link inhibitory sensorimotor gating (PPI) with a range of cognitive inhibition measures was not successful (Swerdlow et al 1995a).

Reductions in PPI have been demonstrated in various clinical conditions in which impaired cognitive, motor, or sensorimotor inhibition as well as deficient functioning of CSPP brain circuits are commonly implied: schizophrenia (e.g., Braff et al 1978, 1992; Bolino et al 1994; Kumari et al 2000; Weike et al 2000; Parwani et al 2000), schizotypal personality disorder (Cadenhead et al 1993), Huntington's disease (Swerdlow et al 1995b), Tourette syndrome (Castellanos et al 1996), and Asperger's syndrome (McAlonan et al 2002). Empirical evidence for a likewise impairment in patients with OCD, however, is still scarce and least conclusive.

In a preliminary assessment of sensorimotor gating in OCD, Swerdlow et al (1993) reported deficient PPI in a small group of 11 patients. Swerdlow et al (1993) observed deficient PPI in OCD patients with 4-dB(A) prepulse intensity (above background) but not with 16-dB(A) prepulses. As the authors acknowledged, this pattern differs from the loss of PPI in most of the other patient groups, all of whom demonstrate PPI impairments with the most intense PP [16 dB(A)]. In fact, Swerdlow et al (1994) later reported in an abstract less PPI in OCD patients over a range from 2-16-dB(A) prepulse intensities and no significant interaction with prepulse intensity.

To summarize, the evidence on PPI in obsessive-compulsive disorder is rather scarce, despite the strong neurobiological plausibility for a PPI deficit in OCD. This study was designed to investigate sensorimotor gating through PPI in a larger sample of OCD patients in order to replicate the preliminary findings (Swerdlow et al 1993) and to explore some possible clinical correlates.

Methods and Materials

Subjects

Written informed consent was obtained from 34 OCD outpatients and 33 healthy control subjects (see Table 1), who were matched for age, sex, and verbal IQ. All patients met diagnostic criteria for obsessive-compulsive disorder according to the DSM-IV (American Psychiatric Association 1994). All participants underwent structured clinical interviews using the Schedule for Affective Disorders and Schizophrenia—Lifetime Version Modified for the Study of Anxiety Disorders (SADS-LA). Healthy control subjects must have been free of a lifetime history of psychiatric and neurologic disease. Exclusion criteria for OCD patients demanded the absence of any other Axis I or II psychiatric disorder (except for comorbid major depression), significant medical or neurologic illness, history of substance abuse or dependence (excluding nicotine and caffeine), or any history of head trauma or loss of consciousness. The study protocol was approved by the Ethics Committee of the Medical Faculty of the University of Bonn.

Table 1. Demographic Data and Rating Scales (Mean ± SEM)

	OCD	Control
n	30	30
Gender (f/m)	15/15	15/15
Smoking[a] (y/n)	10/20	15/15
Age	32.2 ± 1.4	30.8 ± 2.1
Verbal IQ	109.1 ± 2.2	109.6 ± 1.8
YBOCS	16.9 ± 1.8	
YBOCS-O	8.4 ± 1.2	
YBOCS-C	8.4 ± 1.1	
BDI	13.1 ± 1.9	
AoO (years)	18.2 ± 1.9	

[a] $\chi^2 = 1.71$, $p = 0.19$; OCD, obsessive-compulsive disorder; YBOCS, Yale-Brown Obsessive-Compulsive Scale-obsession (O) and compulsion (C); BDI, Beck Depression Inventory; AoO, age of illness onset.

Using the Yale-Brown Obsessive-Compulsive Scale (YBOCS; Goodman et al 1989), psychopathology ratings were performed on the day of testing to assess overall OCD severity as well as obsession and compulsion subtotals (YBOCS-O and YBOCS-C, respectively). Since depression is the highest co-occurring psychopathology in OCD (Barlow 1988; Rasmussen and Tsuang 1986), symptoms of depression were also assessed using Beck's Depression Inventory (BDI; Hautzinger et al 1995). In addition, an assessment of verbal intellectual functioning was done in each participant (Schmidt and Metzler 1992).

Except for four patients who were unmedicated, all OCD patients were on a stable medication: exclusively with SSRIs ($n = 12$); with tricyclic substances exclusively (TCS; $n = 4$) or in combination with SSRIs ($n = 2$); or with antipsychotics (APS) in combination with SSRIs ($n = 8$).

Three healthy subjects and four OCD patients were dropped from further analysis because they were found to be nonstartlers (mean PA amplitude of first block < 25 units) according to the criteria of Braff et al (1992). The excluded OCD patients did not differ from the remaining OCD patients in terms of clinical symptomatology (obsessions, compulsions, depression) or with respect to demographic characteristics or age of illness onset.

Startle Response Measurement

All participants initially underwent a brief hearing screening to ensure hearing function within normal limits. Participants were excluded on the basis of hearing impairment at 40 dB(A) (1000 Hz). All subjects passed this screening.

The participants were comfortably seated in a chair next to the recording equipment. They were informed that they would hear white noise and bursts over the headphones and asked to look straight ahead and keep their eyes open during the test session. The eyeblink component of the acoustic startle response (ASR) was assessed by recording the electromyogram (EMG) of the right orbicularis oculi muscle. EMG activity was amplified and digitized with a commercially available computerized startle response monitoring system (EMG-SR-LAB; San Diego Instru-