

Commentary

Obsessive Compulsive and Related Disorders: From the Biological Basis to a Rational Pharmacological Treatment

Gabriele Sachs, Andreas Erfurth

Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria (Dr Sachs); 6th Psychiatric Department, Otto-Wagner-Spital, Vienna, Austria (Dr Erfurth)

Correspondence: Gabriele Sachs, MD, PhD, Department of Psychiatry and Psychotherapy, Medical University of Vienna, Währinger Gürtel 18–20, 1090 Vienna, Austria (gabriele.sachs@meduniwien.ac.at).

Keywords: obsessive compulsive and related disorders, comorbidity, serotonin, neurocognition, personalized treatment

For the clinician, obsessive compulsive and related disorders (OCDs) as defined by the DSM-5 (American Psychiatric Association, 2013) are highly challenging. Treatment response, both to medication and/or psychotherapy, can be slow and incomplete (Perugi et al., 1997; Pallanti and Quercioli, 2006; Phillips and Hollander, 2008; Saxena, 2011; Van Ameringen et al., 2014; Skapinakis et al., 2016). The reasons for this are manifold and include the following:

- a. As we know from the pre-pharmacological era of psychiatry (Westphal, 1877; Thomsen, 1895; Janet, 1903), OCDs including obsessive-compulsive disorder (OCD) are often lifespan disorders. This means that achieving full recovery through treatment is difficult to start with.
- b. Symptoms, including core symptoms of OCDs, are multiple and to some extent unspecific. Already Janet pointed out that “forced agitations” are central characteristics of OCD: “symptoms that are closely related to, but yet cannot properly be called, obsessions and compulsions” (Pitman, 1987).
- c. OCDs including OCD often are comorbid with other psychiatric disorders (Hasler et al., 2005), or expressed in other words: psychopathologic features that make individual patients meet the criteria for OCDs frequently are part of a broad cluster of clinical characteristics that let the same patient also meet the criteria for, for example, bipolar disorder (Angst et al., 2004, 2005; Fineberg et al., 2013), major depression (Degonda et al., 1993), cyclothymia (Hantouche et al., 2003; Perugi et al., 2017), schizophrenia (Poyurovsky et al., 2003; de Haan et al., 2013), impulse control disorder (Issler et al., 2010), anxiety disorder, particularly social phobia (Perugi et al., 1999), or autism spectrum disorder (Vannucchi et al., 2014; Tsuchiyagaito et al., 2017; Wikramanayake et al., 2017).

Fineberg and colleagues (2017) have chosen an innovative and highly promising approach: focusing on compulsive activity in a broad range of disorders, a comprehensive review of cognitive domains, neural circuitry, and treatment of OCDs is provided. This mapping should be understood as stimulus and starting point for further neurobiological and clinical research on OCDs:

- a. Regulation of presynaptic and postsynaptic serotonin (Gardier et al., 1992, 2013; Erfurth et al., 1994; Spies et al., 2015; James et al., 2017; Kraus et al., 2017) is a central strategy in psychopharmacology. Selective serotonin reuptake inhibitors (SSRIs) are a leading option in the treatment of major depression (Schatzberg, 1996; Dold et al., 2016; Novak and Erfurth, 2017), anxiety disorders (Kasper, 2006), and OCDs including OCD (Soomro et al., 2008). While major depression can respond also to a variety of other interventions (e.g., noradrenaline reuptake inhibition, serotonin receptor antagonism), OCD so far has shown reliable clinical response only to pharmacological interventions that strongly increase serotonin within the synaptic cleft. Under these circumstances, it is interesting that the finding of impaired motor inhibition as a key neuroendophenotype in OCD suggests a role for the neuromodulatory influence of the noradrenergic, but not serotonergic system. Would the presence of impaired motor inhibition in an individual OCD patient be a risk factor for SSRI nonresponse? Would a clinical screening for impaired motor inhibition be able to identify possible nonresponders to selective serotonin reuptake inhibition? Would these patients profit from a dual reuptake inhibition strategy, for example, from selective serotonin and noradrenaline reuptake inhibitors (Denys et al., 2007; Dougherty et al., 2015) or from treatment with the strong,

but not selective, serotonin reuptake inhibitor clomipramine (Greist et al., 1990), with its mainly noradrenergic metabolite, desmethylclomipramine, or even monoamine oxidase inhibitors (Carrasco et al., 1992; Erfurth and Schmauss, 1993)?

- b. OCD patients often show cognitive dysfunction (Aigner et al., 2007; Abramovitch et al., 2013; Brennan and Flessner, 2015; Fineberg et al., 2015; Liu et al., 2017), a psychopathological feature, which in general is clearly linked to reductions in functional outcome and quality of life (Sachs et al., 2012; Perna et al., 2016). In particular, executive function has been shown to predict cognitive-behavioral therapy response in childhood obsessive-compulsive disorder (Hybel et al., 2017). Would a thorough examination (“mapping”) of cognitive domains in OCDs be able to contribute to a stratified therapeutic approach? Which role should cognitive remediation, cognitive training, or cognitive enhancement through psychopharmacology have in this context?
- c. Some individuals diagnosed with OCDs might profit from a combination therapy of serotonin reuptake inhibitors with other pharmacological agents (Hirschtritt et al., 2017) including antipsychotics (Dold et al. 2013). So far, such add-on-strategies have often been used in patients with partial response or with psychiatric comorbidity. To give an example: agitation is a central challenge in clinical psychiatry (Garriga et al., 2016; Erfurth, 2017; Amodeo et al., 2017); while serotonergic neurotransmission is clearly linked to agitation and aggression (Kavoussi et al., 1997; Erfurth and Sachs, 2017), SSRIs might not suffice to treat Janet’s “forced agitations” in OCD. In clinical practice, the adjunctive use of anticonvulsants such as valproate, gabapentin, or pregabalin might be helpful (Perugi et al., 2002; Raja and Azzoni, 2004; Onder et al., 2008; Oulis et al., 2011) in treating individual OCD patients with and without bipolar comorbidity. Could examination of neural circuitry and cognitive domains identify patients early on that would profit from such add-on approaches?
- d. Reliable knowledge of the neuroanatomical basis of OCD symptoms and of neuropsychological endophenotypes could lead to further develop and/or refine nonpharmacological treatment strategies, in particular rapid transcranial magnetic stimulation (Giupponi et al., 2009; Lee et al., 2017), transcranial direct current stimulation (Dell’Osso et al., 2017; Fettes et al., 2017), and deep brain stimulation (Höflich et al., 2013; Alonso et al., 2015; Naesström et al., 2016).

In conclusion, understanding neurocognitive domains and neural circuitry of OCD symptoms as reviewed by Fineberg et al. (2017) might help to develop better and more personalized treatment recommendations. This understanding might also contribute to validate the diagnostic categories proposed by DSM-5 and to better comprehend the obvious clinical overlap of OCDs with affective disorders.

Statement of Interest

None.

References

- Abramovitch A, Abramowitz JS, Mittelman A (2013) The neuropsychology of adult obsessive-compulsive disorder: a meta-analysis. *Clin Psychol Rev* 33:1163–11671.
- Aigner M, Sachs G, Bruckmüller E, Winklbaur B, Zitterl W, Kryspin-Exner I, Gur R, Katschnig H (2007) Cognitive and emotion recognition deficits in obsessive-compulsive disorder. *Psychiatry Res* 149:121–128.
- Alonso P, Cuadras D, Gabriëls L, Denys D, Goodman W, Greenberg BD, Jimenez-Ponce F, Kuhn J, Lenartz D, Mallet L, Nuttin B, Real E, Segalas C, Schuurman R, du Montcel ST, Menchon JM (2015) Deep brain stimulation for obsessive-compulsive disorder: a meta-analysis of treatment outcome and predictors of response. *PLoS One* 10:e0133591.
- American Psychiatric Association (2013) *Diagnostic and statistical manual of mental disorders*. 5th ed. Washington, DC: American Psychiatric Association.
- Amodeo G, Fagiolini A, Sachs G, Erfurth A (2017) Older and newer strategies for the pharmacological treatment of agitation in schizophrenia and bipolar disorder. *CNS Neurol Disord Drug Targets* 16 doi: 10.2174/1871527316666170919115507.
- Angst J, Gamma A, Endrass J, Goodwin R, Ajdacic V, Eich D, Rössler W (2004) Obsessive-compulsive severity spectrum in the community: prevalence, comorbidity, and course. *Eur Arch Psychiatry Clin Neurosci* 254:156–164.
- Angst J, Gamma A, Endrass J, Hantouche E, Goodwin R, Ajdacic V, Eich D, Rössler W (2005) Obsessive-compulsive syndromes and disorders: significance of comorbidity with bipolar and anxiety syndromes. *Eur Arch Psychiatry Clin Neurosci* 255:65–71.
- Brennan E, Flessner C (2015) An interrogation of cognitive findings in pediatric obsessive-compulsive and related disorders. *Psychiatry Res* 227:135–143.
- Carrasco JL, Hollander E, Schneier FR, Liebowitz MR (1992) Treatment outcome of obsessive compulsive disorder with comorbid social phobia. *J Clin Psychiatry* 53:387–391.
- Degonda M, Wyss M, Angst J (1993) The Zurich Study. XVIII. Obsessive-compulsive disorders and syndromes in the general population. *Eur Arch Psychiatry Clin Neurosci* 243:16–22.
- De Haan L, Sterk B, Wouters L, Linszen DH (2013) The 5-year course of obsessive-compulsive symptoms and obsessive-compulsive disorder in first-episode schizophrenia and related disorders. *Schizophr Bull.* 39:151–160.
- Dell’Osso B, Cremaschi L, Oldani L, Altamura AC (2017) New directions in the use of brain stimulation interventions in patients with obsessive-compulsive disorder. *Curr Med Chem*. doi: 10.2174/0929867324666170505113631.
- Denys D, Van Nieuwerburgh F, Deforce D, Westenberg HG (2007) Prediction of response to paroxetine and venlafaxine by serotonin-related genes in obsessive-compulsive disorder in a randomized, double-blind trial. *J Clin Psychiatry* 68:747–753.
- Dold M, Aigner M, Lanzenberger R, Kasper S (2013) Antipsychotic augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: a meta-analysis of double-blind, randomized, placebo-controlled trials. *Int J Neuropsychopharmacol.* 16:557–574.
- Dold M, Kautzky A, Bartova L, Rabl U, Souery D, Mendlewicz J, Porcelli S, Serretti A, Zohar J, Montgomery S, Kasper S (2016) Pharmacological treatment strategies in unipolar depression in European tertiary psychiatric treatment centers: a pharmacoepidemiological cross-sectional multicenter study. *Eur Neuropsychopharmacol* 26:1960–1971.
- Dougherty DD, Corse AK, Chou T, Duffy A, Arulpragasam AR, Deckersbach T, Jenike MA, Keuthen NJ (2015) Open-label study of duloxetine for the treatment of obsessive-compulsive disorder. *Int J Neuropsychopharmacol* 18:pyu062.

- Erfurth A (2017) Agitation: a central challenge in psychiatry. *World J Biol Psychiatry* 18:3–4.
- Erfurth A, Gardier AM, Ribeiro E, Wurtman RJ (1994) Effects of subchronic pretreatment with D-fenfluramine or p-chloroamphetamine on [3H]inositolmonophosphate accumulation in rat cortical miniprisms. *Brain Res* 665:107–114.
- Erfurth A, Sachs G (2017) [Aggression and serotonergic dysfunction]. *Psychoprax Neuroprax* 20:23–27.
- Erfurth A, Schmauss M (1993) [Monoamine oxidase inhibitors in the treatment of obsessive disorders. Two case reports and review of the literature]. *Nervenarzt* 64:70–72.
- Fettes P, Schulze L, Downar J (2017) Cortico-striatal-thalamic loop circuits of the orbitofrontal cortex: promising therapeutic targets in psychiatric illness. *Front Syst Neurosci* 11:25.
- Fineberg NA, Hengartner MP, Bergbaum C, Gale T, Rössler W, Angst J (2013) Lifetime comorbidity of obsessive-compulsive disorder and sub-threshold obsessive-compulsive symptomatology in the community: impact, prevalence, socio-demographic and clinical characteristics. *Int J Psychiatry Clin Pract* 17:188–196.
- Fineberg NA, Day GA, de Koenigswarter N, Reghunandanan S, Kolli S, Jefferies-Sewell K, Hranov G, Laws KR (2015) The neuropsychology of obsessive-compulsive personality disorder: a new analysis. *CNS Spectr* 20:490–499.
- Fineberg NA, Apergis-Schoute AM, Vaghi MM, Banca P, Gillan CM, Voon V, Chamberlain SR, Cinosi E, Read J, Shahper S, Bullmore ET, Sahakian BJ, Robbins TW (2017) Mapping compulsivity in the DSM-5 obsessive compulsive and related disorders: cognitive domains, neural circuitry and treatment. *Int J Neuropsychopharmacol* doi: 10.1093/ijnp/pyx088.
- Gardier AM (2013) Antidepressant activity: contribution of brain microdialysis in knock-out mice to the understanding of BDNF/5-HT transporter/5-HT autoreceptor interactions. *Front Pharmacol* 4:98.
- Gardier AM, Kaakkola S, Erfurth A, Wurtman RJ (1992) Effects of methiothepin on changes in brain serotonin release induced by repeated administration of high doses of anorectic serotonergic drugs. *Brain Res* 588:67–74.
- Garriga M, et al. (2016) Assessment and management of agitation in psychiatry: expert consensus. *World J Biol Psychiatry* 17:86–128.
- Giupponi G, Pycha R, Dell'Osso B, Pompili M, Walpoth M, Hausmann A, Di Pauli J, Erfurth A, Conca A (2009) Neurophysiological and neuropsychiatric aspects of transcranial magnetic stimulation. *Clinical Neuropsychiatry* 6:234–245.
- Greist JH, Jefferson JW, Rosenfeld R, Gutzmann LD, March JS, Barklage NE (1990) Clomipramine and obsessive compulsive disorder: a placebo-controlled double-blind study of 32 patients. *J Clin Psychiatry* 51:292–297.
- Hantouche EG, Angst J, Demonfaucon C, Perugi G, Lancrenon S, Akiskal HS (2003) Cyclothymic OCD: a distinct form? *J Affect Disord* 75:1–10.
- Hasler G, LaSalle-Ricci VH, Ronquillo JG, Crawley SA, Cochran LW, Kazuba D, Greenberg BD, Murphy DL (2005) Obsessive-compulsive disorder symptom dimensions show specific relationships to psychiatric comorbidity. *Psychiatry Res* 135:121–132.
- Hirschtritt ME, Bloch MH, Mathews CA (2017) Obsessive-compulsive disorder: advances in diagnosis and treatment. *JAMA* 317:1358–1367.
- Höflich A, Savli M, Comasco E, Moser U, Novak K, Kasper S, Lanzenberger R (2013) Neuropsychiatric deep brain stimulation for translational neuroimaging. *Neuroimage* 79:30–41.
- Hybel KA, Mortensen EL, Lambek R, Højgaard DRMA, Thomsen PH (2017) Executive function predicts cognitive-behavioral therapy response in childhood obsessive-compulsive disorder. *Behav Res Ther* 99:11–18.
- Issler CK, Monkul ES, Amaral JA, Tamada RS, Shavitt RG, Miguel EC, Lafer B (2010) Bipolar disorder and comorbid obsessive-compulsive disorder is associated with higher rates of anxiety and impulse control disorders. *Acta Neuropsychiatr* 22:81–86.
- James GM, Baldinger-Melich P, Philippe C, Kranz GS, Vanicek T, Hahn A, Gryglewski G, Hienert M, Spies M, Traub-Weidinger T, Mitterhauser M, Wadsak W, Hacker M, Kasper S, Lanzenberger R (2017) Effects of selective serotonin reuptake inhibitors on interregional relation of serotonin transporter availability in major depression. *Front Hum Neurosci* 11:48.
- Janet P (1903) *Les Obsessions et la Psychasthénie*. Paris: Félix Alcan.
- Kavoussi R, Armstead P, Coccaro E (1997) The neurobiology of impulsive aggression. *Psychiatr Clin North Am.* 20:395–403.
- Kasper S (2006) Anxiety disorders: under-diagnosed and insufficiently treated. *Int J Psychiatry Clin Pract* 10:3–9.
- Kraus C, Castrén E, Kasper S, Lanzenberger R (2017) Serotonin and neuroplasticity: links between molecular, functional and structural pathophysiology in depression. *Neurosci Biobehav Rev* 77:317–326.
- Lee YJ, Koo BH, Seo WS, Kim HG, Kim JY, Cheon EJ (2017) Repetitive transcranial magnetic stimulation of the supplementary motor area in treatment-resistant obsessive-compulsive disorder: an open-label pilot study. *J Clin Neurosci* 44:264–268.
- Liu W, Fan J, Gan J, Lei H, Niu C, Chan RCK, Zhu X (2017) Disassociation of cognitive and affective aspects of theory of mind in obsessive-compulsive disorder. *Psychiatry Res* 255:367–372.
- Naesström M, Blomstedt P, Bodlund O (2016) A systematic review of psychiatric indications for deep brain stimulation, with focus on major depressive and obsessive-compulsive disorder. *Nord J Psychiatry* 70:483–491.
- Novak W, Erfurth A (2017) [Treatment of depressive disorders with selective serotonin reuptake inhibitors (SSRI)]. *Psychoprax Neuroprax* 20:28–41.
- Onder E, Tural U, Gökbakan M (2008) Does gabapentin lead to early symptom improvement in obsessive-compulsive disorder? *Eur Arch Psychiatry Clin Neurosci* 258:319–323.
- Oulis P, Mourikis I, Konstantakopoulos G (2011) Pregabalin augmentation in treatment-resistant obsessive-compulsive disorder. *Int Clin Psychopharmacol* 26:221–224.
- Pallanti S, Quercioli L (2006) Treatment-refractory obsessive-compulsive disorder: methodological issues, operational definitions and therapeutic lines. *Prog Neuropsychopharmacol Biol Psychiatry* 30:400–412.
- Perna G, Cavedini P, Harvey PD, Di Chiaro NV, Daccò S, Caldirola D (2016) Does neuropsychological performance impact on real-life functional achievements in obsessive-compulsive disorder? A preliminary study. *Int J Psychiatry Clin Pract* 20:224–231.
- Perugi G, Akiskal HS, Ramacciotti S, Nassini S, Toni C, Milanfranchi A, Musetti L (1999) Depressive comorbidity of panic, social phobic, and obsessive-compulsive disorders re-examined: is there a bipolar II connection? *J Psychiatr Res* 33:53–61.
- Perugi G, Giannotti D, Frare F, Vaio SD, Valori E, Maggi L, Cassano GB, Akiskal HS (1997) Prevalence, phenomenology and comorbidity of body dysmorphic disorder (dysmorphophobia) in a clinical population. *Int J Psychiatry Clin Pract* 1:77–82.

- Perugi G, Toni C, Frare F, Traverso MC, Hantouche E, Akiskal HS (2002) Obsessive-compulsive-bipolar comorbidity: a systematic exploration of clinical features and treatment outcome. *J Clin Psychiatry* 63:1129–1134.
- Perugi G, Hantouche E, Vannucchi G (2017) Diagnosis and treatment of cyclothymia: the “primacy” of temperament. *Curr Neuropsycharmacol* 15:372–379.
- Phillips KA, Hollander E (2008) Treating body dysmorphic disorder with medication: evidence, misconceptions, and a suggested approach. *Body Image* 5:13–27.
- Pitman RK (1987) Pierre Janet on obsessive-compulsive disorder (1903). Review and commentary. *Arch Gen Psychiatry* 44:226–232.
- Poyurovsky M, Kriss V, Weisman G, Faragian S, Kurs R, Schneidman M, Fuchs C, Weizman A, Weizman R (2003) Comparison of clinical characteristics and comorbidity in schizophrenia patients with and without obsessive-compulsive disorder: schizophrenic and OC symptoms in schizophrenia. *J Clin Psychiatry* 64:1300–1307.
- Raja M, Azzoni A (2004) Clinical management of obsessive-compulsive-bipolar comorbidity: a case series. *Bipolar Disord* 6:264–270.
- Sachs G, Winklbaur B, Jagsch R, Lasser I, Kryspin-Exner I, Frommann N, Wölwer W (2012) Training of affect recognition (TAR) in schizophrenia--impact on functional outcome. *Schizophr Res* 138:262–267.
- Saxena S (2011) Pharmacotherapy of compulsive hoarding. *J Clin Psychol* 67:477–484.
- Schatzberg AF (1996) Treatment of severe depression with the selective serotonin reuptake inhibitors. *Depress Anxiety* 4:182–189.
- Skapinakis P, Caldwell DM, Hollingworth W, Bryden P, Fineberg NA, Salkovskis P, Welton NJ, Baxter H, Kessler D, Churchill R, Lewis G (2016) Pharmacological and psychotherapeutic interventions for management of obsessive-compulsive disorder in adults: a systematic review and network meta-analysis. *Lancet Psychiatry* 3:730–739.
- Soomro GM, Altman D, Rajagopal S, Oakley-Browne M. (2008) Selective serotonin re-uptake inhibitors (SSRIs) versus placebo for obsessive compulsive disorder (OCD). *Cochrane Database Syst Rev*:CD001765.
- Spies M, Knudsen GM, Lanzenberger R, Kasper S (2015) The serotonin transporter in psychiatric disorders: insights from PET imaging. *Lancet Psychiatry* 2:743–755.
- Thomsen R (1895) Klinische Beiträge zur Lehre von den Zwangsvorstellungen und verwandten psychischen Zuständen. *Arch Psychiat Nervenkrankh* 27:319–385.
- Tsuchiyagaito A, Hirano Y, Asano K, Oshima F, Nagaoka S, Takebayashi Y, Matsumoto K, Masuda Y, Iyo M, Shimizu E, Nakagawa A (2017) Cognitive-behavioral therapy for obsessive-compulsive disorder with and without autism spectrum disorder: gray matter differences associated with poor outcome. *Front Psychiatry* 8:143.
- Van Ameringen M, Patterson B, Simpson W (2014) DSM-5 obsessive-compulsive and related disorders: clinical implications of new criteria. *Depress Anxiety* 31:487–493.
- Vannucchi G, Masi G, Toni C, Dell’Osso L, Erfurth A, Perugi G (2014) Bipolar disorder in adults with Asperger’s Syndrome: a systematic review. *J Affect Disord* 168:151–160.
- Westphal CFO (1877) Ueber Zwangsvorstellungen. *Berlin Klin Wochenschrift* 46:669–672 and 47:687–689.
- Wikramanayake WNM, Mandy W, Shahper S, Kaur S, Kolli S, Osman S, Reid J, Jefferies-Sewell K, Fineberg NA (2017) Autism spectrum disorders in adult outpatients with obsessive compulsive disorder in the UK. *Int J Psychiatry Clin Pract* 11:1–9.