



A rheumatologist's perspective on OCD in children

Patrick Whelan MD PhD

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- Lecturer in Pediatrics, *Harvard Medical School*
- Associate Physician, *MassGeneral Hospital for Children*
- Associate Clinical Professor of Pediatrics, *Geffen School of Medicine, UCLA*
- Clinical Assistant Prof., Dept of Molecular Microbiology & Immunology, *Keck School of Medicine at USC*

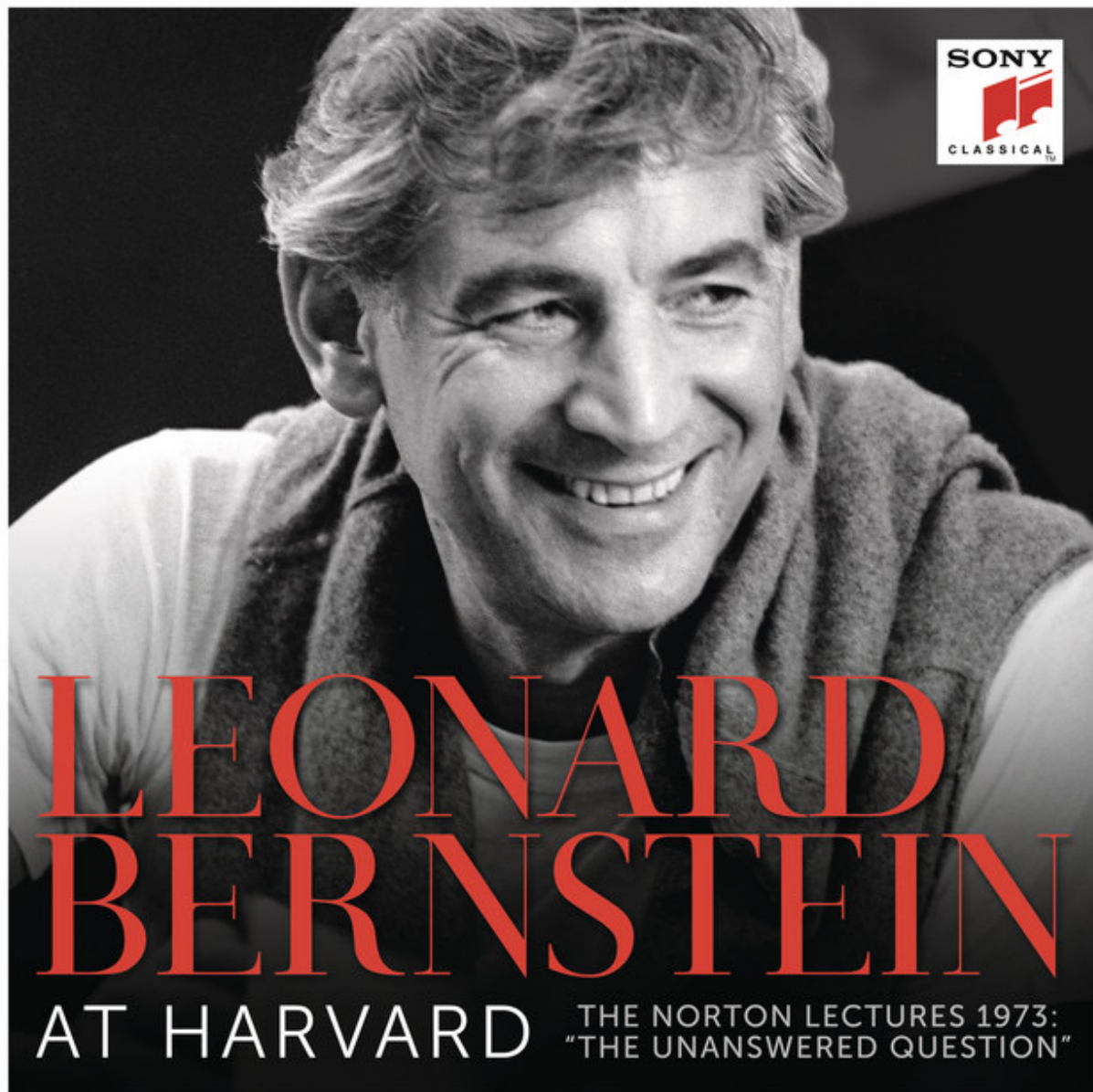


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Psychology
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Music
& the Mind



LEONARD BERNSTEIN

AT HARVARD THE NORTON LECTURES 1973:
"THE UNANSWERED QUESTION"

Aug 25, 1918 to Oct 14, 1990



Music as a model for the stress response

- Music-evoked emotions modulate neural responses in a variety of limbic and paralimbic brain areas that are also activated during emotional experiences in other contexts -- for example, the mesolimbic reward – and thus recruits evolutionarily ancient brain circuits associated with fundamental aspects of affective behavior.
- Tonal music is characterized by a continuous flow of tension and resolution. Imaging with fMRI shows oxygen level-dependent signal increases in the left lateral orbitofrontal cortex (OFC) and in the right superficial amygdala during periods of increasing tension

Tension-related activity in the orbitofrontal cortex and amygdala: an fMRI study with music

Moritz Lehne,¹ Martin Rohrmeier,^{1,2} and Stefan Koelsch¹

¹Cluster of Excellence 'Languages of Emotion', Freie Universität Berlin, Habelschwerdter Allee 45, 14195 Berlin, Germany and ²MIT Intelligence Initiative, Department of Linguistics and Philosophy, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

Tonal music is characterized by a continuous flow of tension and resolution. This flow of tension and resolution is closely related to processes of expectancy and prediction and is a key mediator of music-evoked emotions. However, the neural correlates of subjectively experienced tension and resolution have not yet been investigated. We acquired continuous ratings of musical tension for four piano pieces. In a subsequent functional magnetic resonance imaging experiment, we identified blood oxygen level-dependent signal increases related to musical tension in the left lateral orbitofrontal cortex (pars orbitalis of the inferior frontal gyrus). In addition, a region of interest analysis in bilateral amygdala showed activation in the right superficial amygdala during periods of increasing tension (compared with decreasing tension). This is the first neuroimaging study investigating the time-varying changes of the emotional experience of musical tension, revealing brain activity in key areas of affective processing.

Keywords: music; tension-resolution patterns; fMRI; emotion; expectancy

INTRODUCTION

The processing of music involves a complex machinery of cognitive and affective functions that rely on neurobiological processes of the human brain (Peretz and Zatorre, 2005; Koelsch, 2012; Pearce and Rohrmeier, 2012). The past years have seen a growing interest in using music as a tool to study these functions and their underlying neuronal mechanisms (Zatorre, 2005). Because of its power to evoke strong emotional experiences, music is particularly interesting for affective neuroscience, and an increasing number of neuroimaging studies use music to unveil the brain mechanisms underlying emotion

(Breiter *et al.*, 1996; Morris *et al.*, 1996; Blair *et al.*, 1999), affective pictures (Liberzon *et al.*, 2003; Taylor *et al.*, 2003; Phan *et al.*, 2004), or words (Maddock *et al.*, 2003; Kuchinke *et al.*, 2005). Likewise, the focus on static aspects of emotions is also reflected in neuroimaging studies on music-evoked emotions, which generally assume that an emotional response to a piece of music remains relatively constant over the entire duration of the piece. Neural correlates of music-evoked emotions have, for example, been investigated by contrasting consonant/dissonant (Blood *et al.*, 1999), pleasant/unpleasant (Koelsch *et al.*, 2006), or happy/sad (Khalifa *et al.*, 2005; Mitterschiffthaler *et al.*,

definitions



DSM-5 Criteria for OCD

- ✓ Presence of obsessions, compulsions or both

Obsessions are :

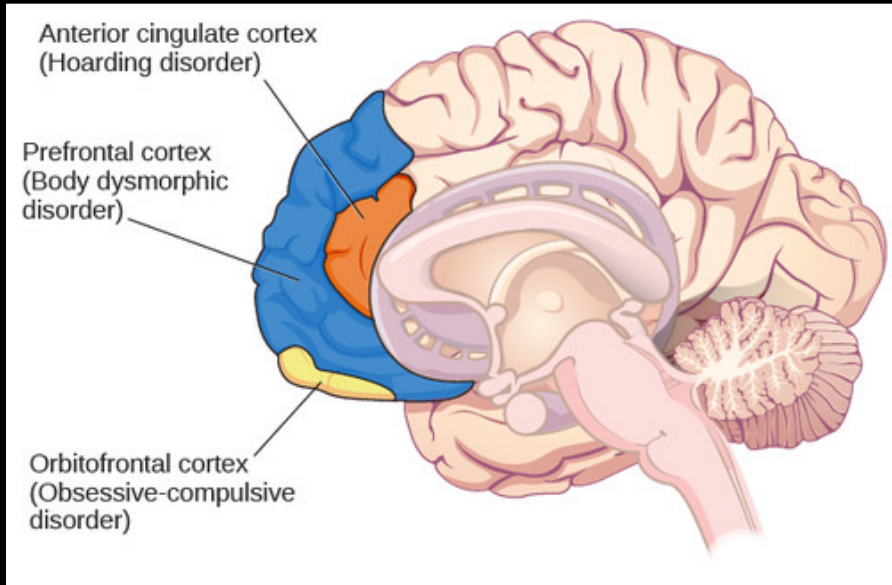
1. Recurrent and persistent thoughts, urges, images that are experienced as intrusive and unwanted, and that in most individuals cause marked anxiety or distress
2. The individual attempts to ignore or suppress such thoughts, urges or images or to neutralize them with some other thought or action

Compulsions are :

1. Repetitive behaviours or mental acts that the individual feels driven to perform in response to an obsession
 2. The behaviours or mental acts are aimed at preventing some dreaded event or situation (but are not connected in a realistic way with what they are designed to neutralize or prevent)
- ✓ The obsessions and compulsions are time consuming or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

ICD10 criteria for OCD

1. Either obsessions or compulsions or both present on most days for a period of 2 weeks.
2. Obsessions (unwanted ideas, images or impulses that repeatedly enter a person's mind) and compulsions (repetitive stereotyped behaviours or mental acts driven by rules that must be applied rigidly) share the following features:
 - ▶ Patient is aware that these originate from their own mind.
 - ▶ They are repetitive, unpleasant and distressing to the patient. At least one is perceived as excessive or unreasonable ('egodystonic').
 - ▶ At least one is resisted unsuccessfully, even though others may be present that the sufferer no longer resists.
 - ▶ Thought of carrying out the obsession or compulsion is not intrinsically pleasurable (simple relief of tension momentarily on completion of the thought/act is not regarded as pleasure in this sense).
3. The symptoms must be disabling. Even young children will have some insight into the senselessness of the thoughts and behaviours.



- Arises from alterations to frontostriatal circuitry
- Hyperactivation of the orbitofrontal cortex proposed to mediate persistent thoughts about threat and harm (obsessions)
- Attempt to neutralize perceived threats (compulsions)
- Increased activation in the lateral and medial orbitofrontal cortex (both children and adults)
- Found in unaffected relatives
Chamberlain et al. Science 2008
- Treatment studies show reduced activation in the OFC after CBT

pathogenesis

etiology

- Twin studies: genetics explains 45%–65% of the variance in pediatric OCD
- Higher heritability in children than in adults
- GWAS indicate polygenic origin, particularly serotonergic, dopaminergic, and glutamatergic systems

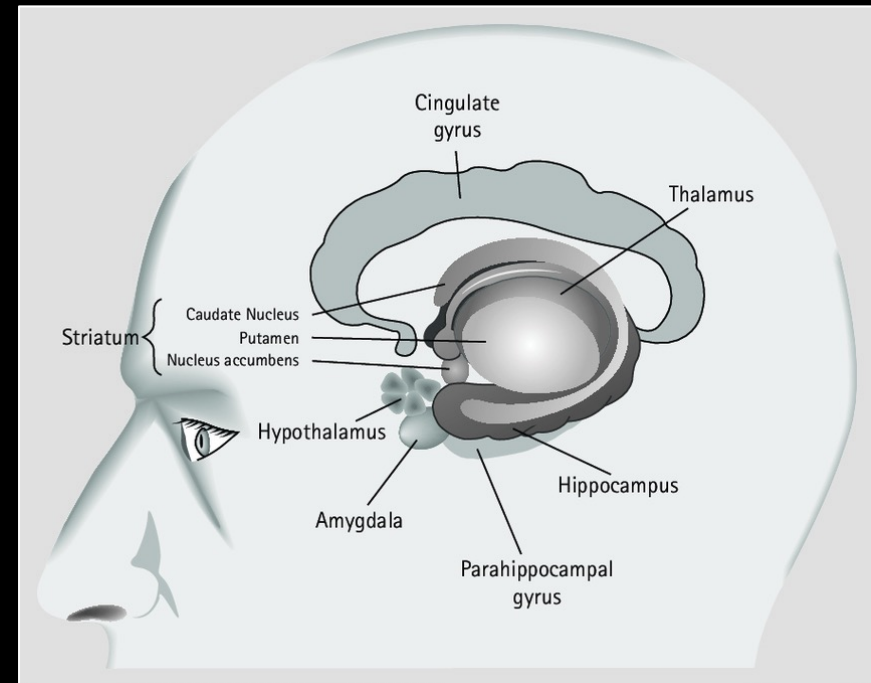


epidemiology

- Pediatric prevalence of 0.25%–4%
- Untreated symptoms wax/wane
- Marked functional impairment across multiple domains, including home, school, and social
- Increased risk of other psychiatric disorders in adulthood

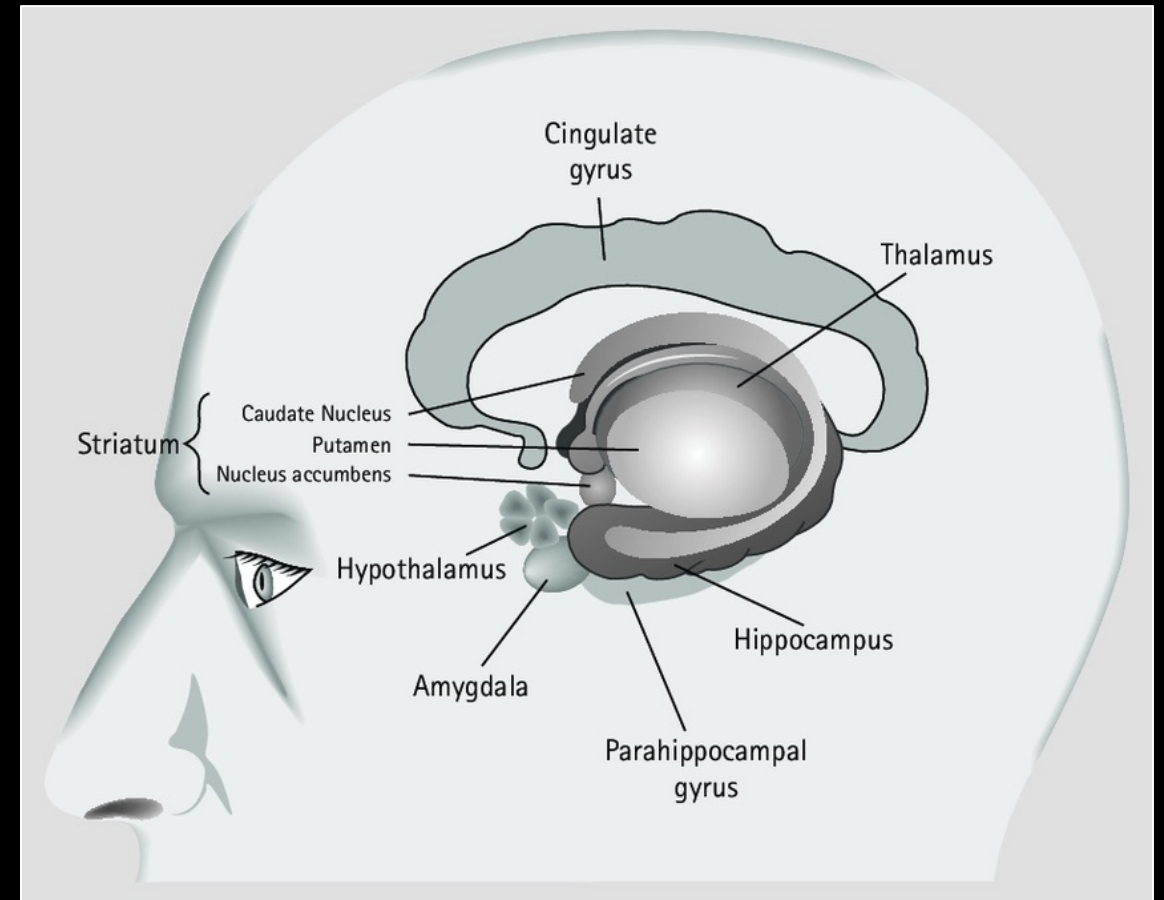
Basal ganglia

Collection of structures important in voluntary movement, but also with important roles in cognition, learning, motivation and other functions. The basal ganglia include the caudate, putamen, substantia nigra, globus pallidus, nucleus accumbens, and subthalamic nucleus



Limbic system

Structures involved in processing emotion and memory, including the hippocampus, amygdala, and the hypothalamus



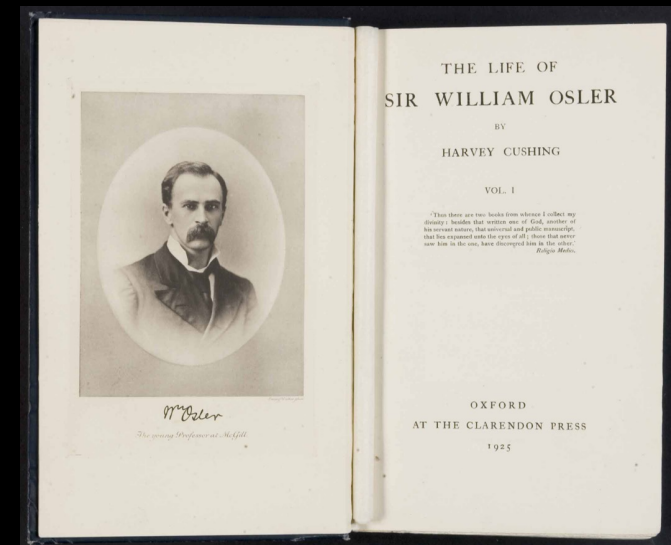


environmental influences

- Social isolation, physical abuse, and negative emotionality predict adult OCD diagnosis *Grisham et al. Psychol Med 2011*
- No association between adverse childhood experiences and OCD *Visser et al. J Clin Psychiatry 2014*

Sir William Osler

- Described the relationship between OCD and tics following *pharyngitis*
- He noted "a certain perseverativeness of behavior" in patients with Sydenham's chorea manifestations of rheumatic fever
- Basal ganglia involvement in
 - Sydenham's chorea
 - OCD
 - Antineuronal antibodies in both



PANDAS

Pediatric
Autoimmune
Neuropsychiatric
Disorders
Associated with
Streptococcal infection

Swedo SE, Leonard HL,
Garvey M, et al. PANDAS:
clinical description of the first
50 cases. *Am J
Psychiatry*.1998; 155 :264





pandas/pans

- More widespread neuropsychiatric difficulties than other children with OCD
 - Enuresis
 - Deterioration in handwriting
 - Impulsivity
- OCD in this population responds as well to standard treatments
- Effectiveness of prophylactic antibiotics is inconsistent

PANDAS: 5 inclusionary criteria

- **Presence of OCD and/or tic disorder**

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- **Pre-pubertal symptom onset**

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- **Sudden onset or episodic course of symptoms**
(typically 7-14 days)

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PANDAS: 5 inclusionary criteria

- Presence of OCD and/or tic disorder
- Pre-pubertal symptom onset
- Sudden onset or episodic course of symptoms
- Temporal association between streptococcal infections and neuropsychiatric symptom exacerbations
- **Associated behavioral abnormalities**

PANS/PANDAS patient survey

165 patients were found to have a differential diagnosis of PANS/PANDAS from June 2021 through June 2022



Preliminary Findings from the first 103 patients:

** Patients had a PANS/PANDAS differential diagnosis if the words “PANS,” “PANDAS,” or “OCD” were mentioned in patients’ initial meeting*

Clinical features

- Of all (103) patients being evaluated for a differential diagnosis of PANS/PANDAS...
- Average age of initial evaluation:
- 57.6% male, 40.6% female, 1.2% non-binary, 0.6% transgender
- **Clinical presentation:**
 - 92.2% had OCD symptoms
 - 70.9% had an *abrupt* onset of OCD-related symptoms
 - 89.3% had significant anxiety or separation anxiety
 - 83.5% had sleep disorders
 - 71.8% had emotional lability
 - 65.7% had tics
 - 56.3% had sensory processing issues
 - 43.7% had restrictive eating
 - 37.9% had enuresis
 - 19.4% had a history of panic attacks



Infection and PANS/PANDAS

- 40.8% experienced infection preceding the onset of their symptoms (not necessarily Strep)

Of all patients with a possible/likely/presumed diagnosis of PANS/PANDAS (79 out of 103 patients):

- **Less than ½ of patients had a clinically significant Strep history**
 - 44.2% had Strep pharyngitis, at some point in their history
 - 19.4% had elevated ASLO or Anti-DNase B results
- Antibiotic treatment alleviated symptoms
 - 79.7% of (possible) PANS patients were prescribed antibiotics
 - **82.4% of patients on antibiotics showed improvement**
 - **60.5% had a history of frequent infections (46 kids out of 76 total)**

Role of group-A beta-hemolytic *Streptococci*

- 9.7% were given a likely or presumed diagnosis of PANDAS [10 kids]
- 90% of these patients had a history of Strep pharyngitis preceding the onset of their behavioral symptoms
- 40% had elevated ASLO or Anti-DNase B strep labs
- 100% of patients had *either* a history of Strep pharyngitis or positive Strep labs
- Only 3 of these patients had a history of both pharyngitis AND elevated Strep labs (30% of the presumed PANDAS patients...**but only 2.9% of all 103 patients with a ddx of PANDAS**)

Pathogenesis

Pathogen + Susceptible Host



Immune Response



Sydenham's chorea or
PANDAS

Differential diagnosis

- Children are less likely than adults to have insight into the irrationality of their obsessions and compulsions
- Reclassification in DSM5: 'OCD and related disorders'
 - body dysmorphic disorder
 - hoarding disorder
 - trichotillomania.

OCD and autism

- Restricted interests and stereotyped behaviors seen in autism
- In contrast to autism-related stereotyped behaviors, compulsions are usually
 - Preceded by an obsession
 - Associated with relief in anxiety
 - Egodystonic (ie, unwanted and inconsistent with the individual's fundamental values)
 - Not intrinsically pleasurable

OCD and tics

- ~60% pediatric OCD meet criteria for a tic disorder
- Earlier age of OCD
- Complex tics difficult to differentiate from compulsions
 - Tics are largely involuntary & simple
 - Compulsions are performed deliberately to relieve anxiety, often elaborate

evaluation

- Careful history & exam
 - Development, tics
 - Infection history (Strep, Covid)
 - Rheumatic disease manifestations
 - Sensory processing
 - Sleep
 - Separation anxiety
 - Disordered eating behavior
 - Enuresis
 - Co-morbidity (self-harm, depression, oppositional behavior)
 - Emotional lability
- Lab testing
 - Immunodeficiency
 - Infection (Strep, mycoplasma, Covid)
 - Endocrine (anti-thyroid abs, TSH, prolactin)
 - Rheumatology (ANA, HLA-B27)

treatment

- Referral for CBT with ERP
 - Sleep modification
 - Tic management strategies
 - NSAIDs (naproxen)
 - Alpha2-agonists (clonidine, guanfacine)
 - Trial of antibiotics
 - Underlying conditions
 - Steroid-responsive encephalopathy
 - Arthritis/IBD
 - Thyroid disorders
 - Psychopharmacology options
 - ASD and ODD respond less well
 - 50% of previous non-responders show benefit from anti-dopamines
- Krebs G, et al. Arch Dis Child 2015;100:495-499*
- IVIg, rituximab, plasmapheresis

Irritability/ ODD

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Irritability in children and adolescents with OCD

Andrew G Guzick¹, Daniel A. Geller², Brent J. Small³, Tanya K. Murphy^{4,5,6}, Sabine Wilhelm², Eric A. Storch¹

¹Baylor College of Medicine, 1977 Butler Blvd., Houston, TX 77030, USA

²Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

³School of Aging Studies, University of South Florida, Tampa, FL, USA

⁴Department of Pediatrics, University of South Florida, St. Petersburg, FL, USA

⁵Department of Psychiatry and Behavioral Neurosciences, University of South Florida, Tampa, FL, USA

⁶Johns Hopkins All Children's Hospital, St. Petersburg, FL, USA

Abstract

Irritability is a common, impairing transdiagnostic symptom in childhood psychopathology, though it has not been comprehensively studied in pediatric obsessive-compulsive disorder (OCD). Further, the central cognitive behavioral treatment component for OCD, exposure and response prevention therapy (ERP), has been recently proposed as a treatment for irritability. This study aimed to evaluate whether certain clinical characteristics are associated with irritability in pediatric OCD and whether irritability reduces following ERP. Participants were 161 youth (ages 7–17) with OCD and a caregiver participating in a randomized controlled trial of D-cycloserine or pill placebo augmented ERP. Participants completed validated assessments during treatment. Irritability was significantly and positively associated with depressive symptoms, defiance, functional impairment, and family accommodation, was negatively related to responsibility for harm/inflated threat estimation beliefs, but was not associated with pretreatment OCD severity, symptom dimensions, perfectionism/need for certainty, or anxiety. Irritability significantly declined following treatment, with over half of youth with any pretreatment irritability experiencing clinically significant change, though this change was not related to OCD improvement. Results suggest that irritability may be a marker of psychiatric comorbidity, parental accommodation, and impairment in youth with OCD. Implications for the exposure-based treatment of irritability are discussed.

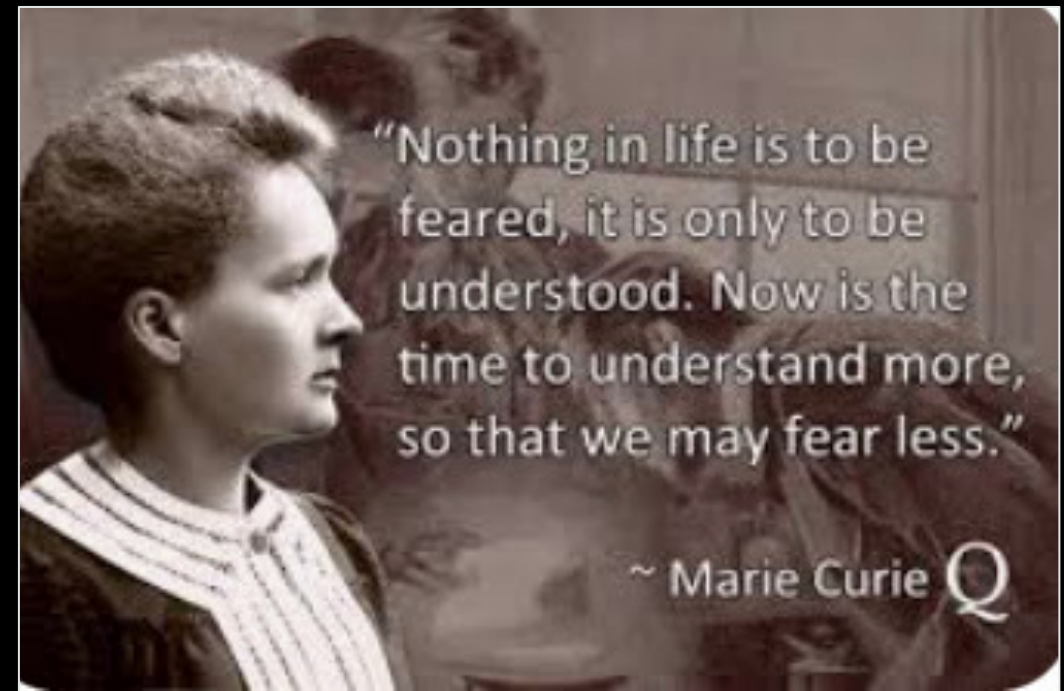
"Whither music in our time?"



"The creative mystery ... is inextricably rooted in the rich earth of our innate response, in those deep, unconscious regions where the universals of tonality and language reside."

Summary

1. OCD is a multigenic disorder with serotonergic, dopaminergic, and glutamatergic components
2. More prevalent in childhood than previously thought
3. Tied principally to hyperactivation of the orbitofrontal cortex -- persistent thoughts about threat and harm (obsessions)
4. No longer an "anxiety disorder" in DSM5
5. Treatment of CBT & drug-refractory OCD can benefit from medical/rheumatologic evaluation and response (eg sleep disorders, endocrine, spondylo)
6. Besides the abruptness of the onset, PANS/PANDAS-assoc OCD characterized by other unique qualities: enuresis, developmental regression, impulsivity





Summary

- Strep infection can lead to arthritis
 - Post-streptococcal
 - Rheumatic Fever
- PANDAS/PANS are a set of controversial neurologic disorders
 - Only 3% of 103 patients had clear PANDAS
 - Nonetheless, 82% of all patients improved on antibiotics
- Now almost 500 families
- PANDAS may be linked to immunodeficiency
 - 61% of all patients had a history of frequent infections
 - Only ~10% of patients progress to IVIg or related therapies