OCD
Clinical expression of OCD is heterogeneous in the types of obsessions and compulsions, heritability, and co-morbid conditions.

- share features with other disorders, termed “OC-spectrum disorders” that include Tourette’s syndrome, trichotillomania, and body dysmorphic disorder, Sydenham chorea (rheumatic fever).

- ego dystonicity– realize thoughts and actions are irrational or excessive

- Must take up more than 1 hour a day. The obsessions and compulsions can go on for hours. For example, a “checker” checks, but cannot be sure and has to check again and again.

- Must disrupt daily routine

- Have an early age of onset. Childhood onset OCD, tends to affect males more than females, tends to be related to motor tic disorders, and may be severe and refractory to standard therapies.

- Symptoms can’t result from effects of other medical conditions or substances

- Some patients suffer mainly obsessions, others mainly compulsions, and still others both. Thus OCD can express itself as primarily a cognitive-affective disorder or primarily an executive behavioral disorder.
Obsessive-Compulsive Disorder: DSM-IV criteria

- Obsessions
  - Recurrent thoughts, images or impulses that are intrusive and cause marked distress.
  - Aggressive, Contamination, Sexual, Religious, Somatic, Symmetry/Order, Hoarding
  - Obsessions are not simply excessive worries.
  - Person tries to suppress or neutralize them
  - Obsessions are initially recognized as part of one’s mind. Not inserted.
Compulsions

- Repetitive behaviors (handwashing, ordering, checking) or

- mental acts (praying, counting, repeating words silently) that the person is driven to perform.

- Compulsions are aimed at reducing distress or preventing some dreaded consequence.

- OCD patients describe that they “have to” act while not “wanting to” act.

Particular compulsive acts are carried out in response to a particular obsession, as if to neutralize the anxiety and negative affect associated with that obsession.
Obsessive-Compulsive Disorder.

Epidemiology

- affects 2-3% of world’s population
- Start anytime from preschool to adulthood
  - Typically between 20-24
- Risk for first degree relatives is 3-12 times greater than for the general population. Concordance among monozygotics tweens is 80%. No candidates genes identified. Aetiological heterogeneity within the disorder.
- many different forms of OCD – differ from person to person
- ¾ have at least one comorbid psychiatric diagnosis.
- Female to male ratio of 6:4
- Symptom profiles vary per country. In the U.S., 50% had obsessions only, 34% had compulsions only, and only 16% had both.
- Better when diagnosed early
- 30% of the patients are refractory to pharmaco–behavioral therapy
OCD: Comorbidity.

• 56% major depression
• 14% Panic disorder
• 14% GAD
• 26% other anxiety disorders.
• Comorbidity is common among pediatric OCD population.
  – ADHD (34%)
  – Major depression (33%)
  – Tourette’s syndrome (18%)
  – Oppositional defiant disorder (17%)
  – Overanxious disorder (16%).
Neuroimmune Dysfunction

PANDAS = pediatric autoimmune neuropsychiatric disorders associated with streptococcal (A) infections.

The etiology of OCD and tics in the PANDAS subgroup is unknown. The obsessions, compulsions, tics, and other neuropsychiatric symptoms seen in these children are postulated to arise from an interaction of these antibodies with neurons of the basal ganglia.

(1) The presence of a tic disorder and/or OCD.
(2) Prepubertal age at onset, usually between 3 and 12 years of age.
(3) Abrupt symptom onset and/or episodic course of symptom severity.
(4) Temporal association between symptom exacerbations and streptococcal infections.
(6) Presence of neurological abnormalities during periods of symptom exacerbation.

The average age at symptom onset in the PANDAS subgroup is nearly 3 years younger than that previously reported for childhood-onset OCD and up to 2 years younger than the average age of onset for tic disorders.
Passive transfer of streptococcus-induced antibodies reproduces behavioral disturbances in a mouse model of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection

K Yaddanapudi1, M Hornig1, R Serge, J De Miranda, A Baghban, G Villar and WI Lipkin
Tic-related OCD

- Earlier age of onset (prepubertal)
- Affects males more than females
- Certain OCD symptoms more common:
  - Tic-like compulsions (touch, tap, or rub)
  - Intrusive violent or aggressive thoughts
  - Worries about symmetry and exactness
  - (Contamination, cleaning, checking were independent of pt’s tic status)
- Rituals done until “Just right”
- Responds less well to SSRIs....OCD.
- improves with dopamine D2 receptor antagonists
OCD circuit.

Abnormal metabolic activity in OFC, ACC, mPFC and caudate nucleus.

Activity at this circuit is increase in OCD patients at rest, accentuated during provocation of symptoms and attenuated following treatment.
1. + feedback loop from OFC and mPFC to the thalamus via the anterior limb of the internal capsule. This pathway is excitatory and bidirectional.

2. CSTC loop (cortex-striatum-thalamus-cortex). This pathway is inhibitory and is thought to serve as a counterweight to the excitatory positive feedback loop. This inhibitory pathway also receives serotonergic projections from the midbrain into the striatum.

3. A component linking portions of the limbic system to the thalamus to the ACC. These connections are hypothesized to contribute to the affective anxiety component of OCD symptoms.

Hypothesis:
Primary pathogenic mechanism is a dysregulation of the basal ganglia and limbic striatal circuitry working in concert with portions of the orbitofrontal and anterior cingulate cortex.
Para tratar OCD refractario.
A functional neuroimaging investigation of deep brain stimulation in patients with obsessive-compulsive disorder.

Preliminary study in patients with obsessive-compulsive disorder treated with electrical stimulation in the inferior thalamic peduncle.

The anteromedial GPi as a new target for deep brain stimulation in obsessive compulsive disorder.

Estriado ventral
Nucleo subtalamico
Inf pedunculo.
Neurotransmitters involved
Very little is known about the neurochemistry of OCD.

- **5-HT:**
  - SSRI agents thus far shown to be effective in the treatment of OCD.
  - Delay of the maximal therapeutic effect of SSRI is longer in OCD than in major depression.

- **5-HT2** receptors in OFC might be involved.
  - Frequencies of the TT genotype for T102C polymorphism and the AA genotype for 1438 G/A polymorphism were significantly higher in patients with severe OCD (Tot et al., 2003).

- **DA**
  - Surplus with DA blockers + SSRI.
  - Obsessions and compulsions on basal ganglia related disorders (tourette’s syndrome).

- Glutamate system:
  - NR2B subunit was reported to be associated with susceptibility to OCD.
  - Association of the 5072G-5988T haplotype of NR2B with OCD.
  - Increased levels of striatal glutamate that normalized following SRI treatment.

- **NO:** higher levels in plasma. Levels correlate with severity of the symptoms.
  - SSRI, DA agents, Glu agents all inhibit synthesis.
Homeobox genes in obsessive-compulsive disorder.

Two regions on chromosomes 15q and 1q. The first SNP is adjacent to NANOGP8, the second SNP is in MEIS2, and the third is 150 kb between PBX1 and LMX1A.

Pilot study on HTR2A promoter polymorphism, -1438G/A (rs6311) and a nearby copy number variation showed association with onset and severity in early onset obsessive-compulsive disorder.

Serotonin 2A receptor, serotonin transporter and dopamine transporter alterations in dogs with compulsive behaviour as a promising model for human obsessive-compulsive disorder.
Treatment

• Only completely curable in rare cases
• Most people have some symptom relief with treatment
• Treatment choices depend on the problem and patients preferences
• Most common treatments:
  – Behavioral Therapy
  – Cognitive Therapy
  – Medication
Cognitive-Behavioral Therapy

• Cognitive: change the way they think to deal with their fears
• Behavioral: change the way they react to “anxiety-provoking” situations
• Exposure and Response Prevention
  – Slowly learning to tolerate anxiety associated with not performing ritual behavior
• Psychotherapy
  – Talking with therapist to discover what causes the anxiety and how to deal with symptoms
• Systematic Desensitization
  – Learning cognitive strategies to deal with anxiety then gradual exposure to feared object
Medication

• Anxiolytic benzodiazepine such as chloradiazepoxide or diazepam → give temporary relief from anxiety but not really effective on obsessions and compulsions

• Antidepressants because of common depression

• Selective Serotonin Reuptake Inhibitors (SSRIs): Most effective drug treatment helping about 60% of patients
  – Ex: fluoxetine, sertraline, escitalopram, paroxetine.
Modelos Animales/ Test

• 8-OHDPAT (5-HT1A agonist). Decrease spontaneous alternation
  – Modela algunos aspectos: indecision y perseveracion.
  – Responde a SSRI (cronico y subcronico) pero no a desipramine (triciclico).
  – No responde a HFS.

• Quinpirole: (D2/D3 agonist)
  – Compulsive checking.
  – Responde a HFS (N. acc, OFC, BLA).
  – NO fue testeado con drogas efectivas en OCD.
• Marble burying:
  – Responde a SSRI pero también a anxiolíticos
  – Modulado por GnRH.
  – Relacionado con aumento de NO
  – Responde a aripiprazole (atyp antipsy) y memantine (NMDA antag)

• Signal attenuation model
  – Camaras operantes: asociacion de comida con presentacion de estimulo. Una vez alcanzado el nivel deseado se presenta el estimulo sin la posibilidad de acceder a la comida. Se testea estimulo + palancas y se ve nivel de respuesta.
  – Responde a SSRI (agudo). 5-HT2C antag. OFC, Striatum. BLA
  – Quinpirole exacerba los sintomas.

• Deer mice (modelo espontaneo):
  – Spontaneous stereotopy(salto vertical, recorrido conservado, rol ).
  – Responde a drogas SSRI pero no triciclicos. Tambien a 5-HT, DA and Glu
  – Circuito OFC, estriado, BLA.
Compulsive behavior in the 5-HT$_{2C}$ receptor knockout mouse

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Fig. 7. Total head dipping each day (summed over three daily trials) was, overall, significantly higher in KO mice, as determined by repeated-measures ANOVA. Post hoc analysis revealed that KO mice (n=5) did more head dipping on Days 2 and 3, compared to WT mice (n=6). * P < .05. Shaded bars represent WT mice, and open bars represent 5-HT$_{2C}$ receptor KO mice.
Marble burying:

The images A, B, and C show marbles on a surface, with arrows pointing to marbles that have been buried. Images D, E, and F depict marbles in a container, with marbles buried in the sand. The graph to the right shows the number of marbles buried out of 20, with significantly more marbles buried in the KO group compared to the WT group (*** indicates a significant difference).
Sapap interact with PSD95 And Shank families in excitatory synapses.
Sapap 3 highly express in the striatum
Figure 2 | Fluoxetine treatment alleviates excessive grooming and anxiety-like behavior. a, Daily fluoxetine treatment over six days reduced...
Deficits in fEPSP increase sensitivity to NMDA fEPSPs

Rescue: lentivirus inj
Sapap3 and Pathological Grooming in Humans: Results From the OCD Collaborative Genetics Study

O.J. Bienvenu,1* Y. Wang,1 Y.Y. Shugart,2 J.M. Welch,3 M.A. Grados,1 A.J. Fyer,4 S.L. Rauch,5 J.T. McCracken,6 S.A. Rasmussen,7 D.L. Murphy,8 B. Cullen,1 D. Valle,9 R. Hoehn-Saric,1 B.D. Greenberg,7 A. Pinto,7 J.A. Knowles,4 J. Piacentini,6 D.L. Pauls,10 K.Y. Liang,11 V.L. Willour,1 M. Riddle,1 J.F. Samuels,1 G. Feng,3 and G. Nestadt1

SAP90/PSD95-associated protein (SAPAP) family proteins are post-synaptic density (PSD) components that interact with other proteins to form a key scaffolding complex at excitatory (glutamatergic) synapses. A recent study found that mice with a deletion of the Sapap3 gene groomed themselves excessively, exhibited increased anxiety-like behaviors, and had cortico-striatal synaptic defects, all of which were preventable with lentiviral-mediated expression of Sapap3 in the striatum; the behavioral abnormalities were also reversible with fluoxetine. In the current study, we sought to determine whether variation within the human Sapap3 gene was associated with grooming disorders (GDs: pathologic nail biting, pathologic skin picking, and/or trichotillomania) and/or obsessive-compulsive disorder (OCD) in 383 families thoroughly phenotyped for OCD genetic studies. We conducted family-based association analyses using the FBAT and GenAssoc statistical packages. Thirty-two percent of the 1,618 participants met criteria for a GD, and 65% met criteria for OCD. Four of six SNPs were nominally associated \( (P < 0.05) \) with at least one GD (genotypic relative risks: 1.6–3.3), and all three haplotypes were nominally associated with at least one GD (permuted \( P < 0.05 \)). None of the SNPs or haplotypes were significantly associated with OCD itself. We conclude that Sapap3 is a promising functional candidate gene for human GDs, though further work is necessary to confirm this preliminary evidence of association.

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Double deletion of melanocortin 4 receptors and SAPAP3 corrects compulsive behavior and obesity in mice

Pin Xu*, Brad A. Grueterb,1, Jeremiah K. Britt, Latisha McDaniel, Paula J. Huntingtona, Rachel Hodgea, Stephanie Tranb, Brittany L. Masond, Charlotte Leced, Linh Vonge, Bradford B. Lowell, Robert C. Malenkab,2, Michael Lutterc,2,3, and Andrew A. Pieperc,2,3

Doble mutante rescata la transmisión Sinaptica en el estriado ventral de los Sapap3 KO.
SLIT and NTRK-like protein-5 (Slitrk5): one-pass TM protein with 2 extracellular Leucine domains, and a carboxy-terminal domain that is similar to Trk neurotrophin receptors. These proteins have been shown to affect neuronal process outgrowth.
Hair loss start at 3 month of age. The penetrance of this phenotype increased with age, and most of the knockout as well as the heterozygous mice were affected. The lesions in heterozygous mice were similar to those in homozygous mice, but their emergence was delayed by 7–9 months.
Co expresa con PSD95 en espinas
Repeated Cortico-Striatal Stimulation Generates Persistent OCD-Like Behavior

Susanne E. Ahmari,1,2,3,4* Timothy Spellman,5 Neria L. Douglass,1,2 Mazen A. Kheirbek,1,2 H. Blair Simpson,1,3,4 Karl Deisseroth,6 Joshua A. Gordon,1,2 René Hen1,2

[Diagram of brain with labels and arrows indicating different regions and processes]

E

Groom 1 hr post

Control    |    ChR2

Time (sec)

F

Groom chronic

Control    |    ChR2

Time (sec)
**A** Cohort 1: Fluoxetine → Washout

- Fluoxetine 18mg/kg
- Test Days ↓
- Stim

T₀ T₆ T₇ T₁₃ T₁₄ T₂₀ T₂₁ T₂₇ T₂₈ T₃₄
- Habituation 5' daily stim Week 1 Week 2 Washout

**B** 1 hour Post

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<td>Washout</td>
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**C** Cohort 2: Fluoxetine vs. Vehicle

- Vehicle
- Fluoxetine 18mg/kg
- Test Days ↓
- Stim

T₀ T₆ T₇ T₁₃ T₁₄ T₂₀ T₂₁ T₂₇
- Habituation 5' daily stim Week 1 Week 2

**D** 1 hour Post

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*
Optogenetic Stimulation of Lateral Orbitofronto-Striatal Pathway Suppresses Compulsive Behaviors

Eric Burguière¹, Patrícia Monteiro¹, Guoping Feng¹, and Ann M. Graybiel*,¹
¹McGovern Institute for Brain Research and Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139 USA
Búsqueda de estudiantes para tesis de licenciatura y/o doctoral (beca CONICET)

Se buscan estudiantes/graduados de carreras biomédicas con interés en realizar una Tesis de Licenciatura y/o Doctoral con perspectivas a presentarse a Beca tipo I CONICET en el 2014

Lugar:
Laboratorio de Fisiopatología Neuronal, Instituto de Fisiología y Biofísica “Houssay” (UBA-CONICET), Facultad de Medicina - UBA.

Proyecto:

**estudio a nivel conductual, neuropatológico, bioquímico y molecular de nuevos modelos animales basados en la sobreexpresión (animales transgénicos) o knock-down (virus) de TDP-43**, una proteína clave en la patogénesis de enfermedades neurodegenerativas como Esclerosis Lateral Amiotrófica y Demencia Frontotemporal.

Algunas de las **técnicas a utilizar** incluyen (dependiendo del proyecto):
- ensayos conductuales para evaluar fenotipos cognitivos, motores y sociales (inhibitory avoidance, object recognition, Y-maze, open field, plus maze, rotarod, clasping, social recogniton),
- inmunohistoquímica, western blot, microscopía tradicional y confocal
- intervenciones farmacológicas, infusiones virales
- PCR (genotipado), RT-PCR, entre otras.

**Requisitos:**
- tener un promedio mayor o igual a 8 (para presentarse a beca CONICET)
- disponibilidad mínima de 15 hs semanales.

Enviar **Curriculum vitae** actualizado (incluyendo promedio y aplazos) a:

lmuller@fmed.uba.ar

GRACIAS!