INSTITUTO DE PSIQUIATRIA - IPUB
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Tese de Doutorado submetida ao Corpo Docente do Programa de Pós-graduação em Psiquiatria e Saúde Mental -PROPSAM- do Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro, como parte dos requisitos necessários para a obtenção do Grau de Doutor em Psiquiatria.

Orientador: Leonardo Franklin da Costa Fontenelle
Pós-Doutorado

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FENÓTIPOS DO TRANSTORNO OBSESSIVO-COMPULSIVO: EVIDÊNCIAS DE ESTUDOS CLÍNICOS, DE NEUROIMAGEM E NEUROPSICOLOGIA

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Dedicatória

Aos meus pais, que sempre me apoiaram nas minhas escolhas e me ensinaram a ter paciência, ser persistente e nunca desistir dos meus sonhos. Ambos são grandes exemplos em diversos aspectos da vida, principalmente no amor incondicional e companheirismo.

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Resumo

O Transtorno Obsessivo-Compulsivo (TOC) é caracterizado por imagens ou pensamentos intrusivos e repetitivos que causam sofrimento (obsessões) e/ou atos mentais ou motores repetitivos com o objetivo de reduzir a ansiedade ou realizados conforme certas regras (compulsões). É um transtorno crônico e frequente, apesar de um número crescente de estudos acerca do TOC notam-se importantes lacunas na literatura. O presente trabalho busca esclarecer aspectos do TOC no que concerne possíveis subtipos, impacto das comorbidade, perfil neuropsicológico e o envolvimento de regiões/circuitos cerebrais.

No primeiro artigo "Late-onset obsessive-compulsive disorder: risk factors and correlates" publicado no *Journal of Psychiatric Research,* realizamos uma análise multinível dos possíveis aspectos/fatores de risco envolvidos no desenvolvimento do TOC após os 40 anos de idade. Para essa análise, utilizamos um banco de dados de 1001 pacientes com TOC, recrutados junto ao Consórcio Brasileiro de Pesquisa sobre Transtornos do Espectro Obsessivo-Compulsivo (C-TOC). Nossos resultados sugerem que o TOC tardio tem mais chance de ocorrer em mulheres, indivíduos com períodos mais longos de sintomas obsessivo-compulsivos subclínicos e em associação com um importante evento traumático ocorrido após os 40 anos de idade e história de gravidez na própria pessoa ou em alguém próximo.

Em um segundo trabalho no capítulo "Comorbidity in Obsessive-Compulsive and Related Disorders" do volume II do livro "The Wiley Handbook of Obsessive Compulsive Disorders", realizamos uma revisão narrativa de literatura a respeito da comorbidade dos transtornos do espectro obsessivo-compulsivo, incluindo síndrome de tourrete e síndrome de refêrencia olfatória. Este trabalho deixa evidente que a maioria dos pacientes diagnosticados com algum TOC e Transtornos Relacionados possuem pelo menos um outro transtorno do DSM-5 comórbido. As altas taxas de comorbidade podem ser explicadas pela neurobiologia subjacente comum neste grupo ou podem decorrer de problemas inerentes ao sistemas de classificação diagnóstica em psiquiatria nos quais, algumas vezes síndromes são prematuramente elevadas à condição de doenças isoladas, podendo levar a uma visão fragmentada do paciente e a propostas terapêuticas não integradas.

A controvérsia diagnóstica existente na psiquiatria, nos levou a investigar um possível biomarcador capaz de auxiliar no diagnóstico. No artigo "Can Neuroimaging Provide Reliable Biomarkers For Obsessive-Compulsive Disorder? A Narrative Review" publicado na Current Psychiatry Reports foi realizada uma revisão qualitativa da presente literatura de possíveis neurobiomarcadores no TOC. Pudemos observar o papel chave do circuito cortico-estriado-tálamo-cortical (CSTC) e suas conexões límbicas no TOC. Foram identificadas estruturas do CSTC que discriminam pacientes com TOC de controles sadios e de transtornos de ansiedade usando estratégias quantitativas ou qualitativas respectivamente. Finalmente, na avaliação da resposta terapêutica, a espessura do córtex órbito-frontal (OFC) medial direito e esquerdo foi capaz de diferenciar respondedores de não respondedores com uma acurácia em torno de 80%.

Investigando traços impulsivos no TOC e avaliando o modelo de adição comportamental proposto para o TOC, conduzimos o estudo "Subjective and objective impulsivity in obsessive-compulsive disorder" (submetido no Journal of Behavioral Addiction), neste estudo encontramos que a impulsividade no TOC está restrita ao seu componente subjetivo (particularmente impulsividade atencional) diferente do descrito anteriormente. Esses achados sugerem que apesar de se considerarem impulsivos, pacientes adultos com TOC não apresentam evidências objetivas deste comportamento (neuropsicológica).

No último artigo, inspirado no crescimento da neurociência social, apostamos em um estudo mais profundo das emoções morais que pudesse nos ajudar a entender sintomas e disfunções comportamentais observados no TOC. No estudo "Decoding Moral Emotions in Obsessive-Compulsive Disorder" submetido para a revista Neuroimage: Clinical, observamos que a decodificação multivariada da atividade de regiões corticais e subcorticais durante a experiência de culpa, compaixão, nojo e raiva foi capaz de discriminar pacientes com TOC de controles. Além disso, regiões cerebrais em comum ou compartilhadas, incluindo o núcleo acumbens, giro lingual e giro temporal médio, puderam discriminar pacientes com TOC de controles independente de diferentes emoções; e estes correlatos neurais se sobrepõem somente parcialmente com o CSTC, implicado tradicionalmente na pato fisiologia do TOC. Esses achados, consistentes com a conceptualização do TOC como um transtorno

cerebral que envolve diversos circuitos cerebrais, sugerem que o modelo patofisiológico atual pode ser expandido para incorporar novas evidências, que podem apontar para novos objetivos e propostas terapêuticas.

Abstract

Obsessive-Compulsive Disorder (OCD) is characterized by intrusive and repetitive thoughts or images that cause suffering (obsessions) and/or repetitive mental or motor acts aimed to reduce anxiety or performed according to certain rules (compulsions). It is a chronic and frequent disorder; beside the growing number of studies about OCD, there are still important gaps in the literature. This work tries to clarify some aspects of OCD in what concern possible subtypes, impact of comorbidities, neuropsychological profile and the involvement of cerebral regions/circuits.

In the first article: "Late-onset obsessive-compulsive disorder: risk factors and correlates" published in the Journal of Psychiatric Research, we performed a multilevel analysis of the potential aspects/risk factors involved in the development of OCD after 40 years old. We used for this analysis a database of 1001 OCD patients recruited by the Brazilian Consortium of Obsessive-Compulsive Spectrum Disorders (C-TOC). Our results suggest that late-onset OCD is more likely to occur in females, in individuals with long periods of subclinical obsessive-compulsive symptoms, and in association with a major traumatic event occurring after age 40 and a history of recent pregnancy in self or in significant others.

In the second work, in the chapter "Comorbidity in Obsessive-Compulsive and Related Disorders" of the volume II of the book "The Wiley Handbook of Obsessive-Compulsive Disorders", we performed a literature review of the comorbidity of obsessive-compulsive spectrum disorders, including tourrete syndrome and olfactory reference syndrome. This work makes it evident that the majority of the patients diagnosed with any Obsessive-Compulsive and Related Disorders have at least another DSM- 5 comorbid disorder. The high comorbid rates might be explained by the underlying neurobiology shared by this group or result from problems due to the diagnostic classification system in psychiatry, in which sometimes syndromes are prematurely elevated to isolated disorders and might lead to a fragmented view of the patient and to no integrated therapeutic proposals.

The existing diagnostic controversy in psychiatry, lead us to investigate a possible neurobiomarker capable of helping in the diagnostic. In the article "Can Neuroimaging Provide Reliable Biomarkers For Obsessive-Compulsive Disorder? A

Narrative Review" published in Current Psychiatry Reports, we performed a qualitative literature review of the possible neurobiomarkers in OCD. We could observe the key role of the cortico-striatal-thalamus-cortical (CSTC) circuit and its limbic connections in OCD. Structures of the CSTC were identified to be discriminative for OCD patients, healthy controls and anxiety disorders using quantitative and qualitative strategies respectively. Finally, in the evaluation of treatment response, the right and left medial orbito-frontal cortex thickness was capable to differentiate responders from non-responders with accuracy around 80%.

Investigating impulsive traits in OCD and evaluating the behavior addiction model proposed to OCD, we conducted the study "Subjective and objective impulsivity in obsessive-compulsive disorder" (submitted to the Journal of Behavioral Addiction), we found that impulsivity in OCD is restricted to its subjective component (particularly attentional impulsivity) different from what described previously. These findings suggest that even though OCD adult patients consider themselves impulsive, there is no objective evidence of these behavior (neuropsychological).

In the last paper, inspired in the growth of social neuroscience we bet in deeper study of the moral emotions that could help understand compartmental symptoms and dysfunctions observed in OCD. In the study "Decoding Moral Emotions in Obsessive-Compulsive Disorder" submitted to the journal Neuroimage: Clinical, we observed that the multivariate decodification of the cortical and subcortical regions during the experience of guilt, compassion, disgust and anger was capable to discriminate OCD patients from controls. Besides that, brain regions in common or shared, including the nucleus accubens, lingual and medial temporal gyrus, could discriminate OCD patients from controls independently of different emotions; and those neural correlates overlap only partially with the CSTC circuit, traditionally implicated in the pathophysiology of OCD. These findings, consistent with the conceptualization of OCD as a brain disorder that involve different brain circuits, suggest that the current pathophysiological model could be expanded to incorporate new evidence which may indicate to new therapeutic objectives and proposals.

Sumário

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Não há anexos neste trabalho.

1 - Introdução

Classicamente o transtorno obsessivo-compulsivo (TOC) é caracterizado por imagens ou pensamentos intrusivos e repetitivos (obsessões) que causam sofrimento e/ou atos mentais ou motores repetitivos (compulsões) com o objetivo de reduzir a ansiedade ou realizados conforme determinadas regras. Para serem considerados clinicamente significativos, os sintomas do TOC devem ser acompanhados de sofrimento e disfunção importantes, interferindo na rotina ocupacional ou acadêmica, social e de relacionamento interpessoal do sujeito (APA, 2013). Sintomas obsessivos e compulsivos subclínicos são comuns e podem ser identificados no curso normal do desenvolvimento (Rachman and de Silva, 1978).

Segundo os modelos cognitivos, as obsessões tornam-se clinicamente significativas à medida que o pensamento intrusivo é interpretado de forma catastrófica gerando ansiedade e preocupação (Rachman, 1997). A manutenção dos sintomas se daria, em parte, pela crença disfuncional na incapacidade de tolerar ansiedade ou outras emoções como culpa e nojo (Calkins et al., 2013).

Apesar de relatos na literatura documentarem a ocorrência de episódios agudos, o TOC é um transtorno de curso predominantemente crônico (World Health Organization, n.d.). Os sintomas costumam acompanhar os indivíduos ao longo de toda a vida e, muitas vezes, apesar de tratamentos adequados, há manutenção dos sintomas que seguem determinando importante prejuízo nas vidas dos portadores e seus familiares (World Health Organization, n.d.). Além disso, o TOC está associado a elevados custos econômicos diretos e indiretos (Dupont et al., 1995) que são agravados pelo não reconhecimento adequado do transtorno, frequente subdiagnóstico e tratamento inapropriado. Os pacientes podem sentir-se constrangidos de buscar atendimento médico, ou podem não reconhecer que seu problema é passível de ajuda e intervenção. Em estudo com pacientes portadores de TOC foi descrita uma lacuna de 17 anos entre o início dos sintomas e o diagnóstico correto (Hollander et al., 1997).

Estudos epidemiológicos utilizando o Código Internacional de Doenças (CID) sugerem que o TOC é uma condição frequente, com taxa de prevalência em 1 mês

variando de 0,3 até 3,1% (Fontenelle and Hasler 2008). Resultados de estudos transnacionais mostram pouca variação de prevalência entre diferentes populações (Howarth and Weissman 2000). Não há diferença significativa na relação homem-mulher, em contraste com o que se observa nos transtornos de humor e de ansiedade, em que a prevalência é maior em mulheres do que homens (Howarth and Weissman 2000).

A idade de início do TOC tem uma distribuição bimodal. Com um pico de início na puberdade, o início juvenil, especialmente comum em homens, como maior familiaridade e relação com transtorno de tique (Eichstedt and Arnold 2001). E outro mais tardio, com características como por exemplo início após gravidez, aborto ou parto (Abramowitz, Schwartz et al. 2003; Forray, Focseneanu et al. 2010) ou após um evento traumático (Fontenelle et al., 2012).

Pacientes com TOC frequentemente possuem outros transtornos psiquiátricos comórbidos, incluindo transtornos de personalidade. A abertura dos transtornos comórbidos pode preceder, suceder ou ocorrer simultaneamente à abertura do quadro do TOC (Pallanti and Grassi, 2014). Segundo a literatura, as taxas de comorbidades durante a vida de um paciente com TOC variam de 78 a 91% e as taxas de comorbidade atual variam de 42 a 55%, sendo os transtornos de ansiedade e transtorno de humor as mais frequentes (Pallanti and Grassi, 2014).

A chance de um paciente com TOC ter, durante a vida, um episódio de humor é de 64 a 74% e de ter um transtorno de ansiedade como transtorno do pânico, agorafobia, fobia social, fobias específicas, transtorno de ansiedade generalizada de 46 a 52% (Pallanti and Grassi, 2014). Outros transtornos também descritos com frequência são transtorno de tique, transtorno de abuso/ dependência de álcool e/ ou substâncias, transtorno de déficit de atenção hiperatividade, transtornos alimentares e transtornos psicóticos (Pallanti and Grassi, 2014; Petribú, 2001).

A comorbidade com os transtornos do espectro obsessivo-compulsivo, como o transtorno de colecionamento, transtorno de escoriação (skin-picking), tricotilomania e transtorno dismórfico corporal é especialmente importante, havendo importante

sobreposição de diversas características clínicas o que determinou a classificação destes transtornos em um mesmo capítulo na DSM-5 (APA, 2013).

Apesar de ter sido descrito ainda no século XIX, o TOC segue trazendo questões que desafiam a prática clínica e intrigam os pesquisadores, como, por exemplo, a identificação de possíveis marcadores biológicos, a compreensão da diversidade dos sintomas e a investigação de padrões de resposta aos tratamentos disponíveis (Grados and Riddle, 2009). A partir da identificação destes fatores, mais pacientes poderiam se beneficiar de diferentes propostas terapêuticas. Grande parte da dificuldade em responder estas questões pode ser explicada pela heterogeneidade do transtorno. O TOC é um transtorno de etiologia complexa, podendo ser influenciado por diversos fatores genéticos e ambientais.

Neste trabalho abordaremos alguns temas de extrema importância para a compreensão deste transtorno, começando com a possibilidade de identificação de um subtipo de início tardio. Em seguida, abordaremos a importância da comorbidade no transtorno obsessivo-compulsivo e transtornos relacionados e discorrendo acerca da forma atual de formulação diagnóstica e da busca por um possível neurobiomarcador no TOC. Por fim, estudamos o espectro compulsivo-impulsivo e a neurociência social no TOC, e em cima destes assuntos testamos as hipóteses de possíveis traços impulsivos no TOC e da experiência das emoções de culpa, compaixão, nojo e raiva durante um exame de ressonância nuclear magnética nuclear serem capazes de discriminar pacientes com TOC do grupo controle.

2 – Subtipos

O TOC é considerado um transtorno heterogêneo tendo em vista por exemplo, os diferentes tipos de obsessões e compulsões que os pacientes apresentam. Em um tentativa de reduzir tal heterogeneidade, tem sido investigada a possibilidade de identificação de subgrupos mais homogêneos de pacientes de acordo com determinadas características clínicas, tais como idade de início dos sintomas obsessivo-compulsivos (SOC), gênero, comorbidades, ou predominância de dimensões específicas de SOC (verificação/simetria, contaminação/lavagem, agressão/religioso, colecionismo e miscelânea) (Grados and Riddle, 2009). Os sintomas obsessivo-compulsivos podem ser subdivididos em quatro dimensões principais de sintomas. Dimensão de contaminação com rituais de lavagem, de pensamentos de agressão com consequente checagem, simetria com rituais de ordenamento e pensamentos inaceitáveis/ blasfêmia com rituais mentais (Abramowitz et al., 2010).

Os sintomas mais frequentes do TOC são preocupações de contaminação com consequente lavagem e preocupações de agredir alguém ou a si mesmo com consequente checagem (Stein, 2002). Análises fatoriais mostraram subgrupos, com preocupações em relação à simetria e consequentes rituais de arrumação, e um grupo com foco no colecionismo (Leckman et al., 2001). Porém, outros tipos de obsessões e compulsões já foram identificados, como sintomas religiosos, sexuais, somáticos e musicais (Stein et al., 2001). Os sintomas diferem em pacientes com ou sem tiques (Miguel et al., 2001), sugerindo diferenças psicobiológicas.

Apesar de, geralmente, os pacientes reconhecerem seus sintomas como excessivos, o *insight* varia muito, e alguns pacientes são considerados como tendo *insight* pobre (podendo até mesmo estar ausente). Esse subtipo do TOC foi reconhecido pela última edição do DSM através do especificador “com insight pobre” que foi redefinido para permitir a distinção entre indivíduos com insight bom, pobre e ausente/delirante (completa convicção que as crenças do TOC são verdadeiras). Esses pacientes caracterizam-se por apresentar idade de início mais precoce, duração mais longa da doença e maior número de sintomas obsessivo-compulsivos (Kishore et al., 2004).

Além de maior gravidade de sintomas obsessivo-compulsivos, depressivos e ansiosos, prevalência mais elevada de depressão maior e de transtornos de personalidade borderline, narcisista e esquizotípico e menor prevalência de transtorno de personalidade dependente (Türksoy et al., 2002). Ames e colaboradores apontaram ainda a possibilidade de associação do insight pobre com lesões frontais (Ames et al., 1994).

Um especificador incluído no DSM-5, caracterizando outro subtipo do transtorno, foi o "TOC relacionado a tiques", incluindo indivíduos com história crônica de transtorno de tiques associado ao TOC. Tal inclusão caminha em consonância com a crescente literatura acerca deste tema que define este subtipo como uma condição extremamente familiar, com características clínicas específicas, como fenômenos sensoriais (Miguel et al., 2000; Prado et al., 2008) e um curso clínico característico. O argumento mais forte contra este especificador é que crianças com TOC e Transtorno de Tiques crônico respondem igualmente bem a intervenções cognitivas-comportamentais (March et al., 2007). Porém, os casos relacionados com tiques podem ter menos chance de responder a inibidores de recaptação de serotonina sozinhos e têm mais chance de ter maior benefício com a potencialização dos inibidores de recaptação de serotonina com antipsicóticos (Bloch et al., 2006).

Em relação à idade de início, vários estudos vêm reforçando a hipótese do TOC de início precoce como um subgrupo específico de pacientes (do Rosário-Campos et al., 2001). Uma meta-análise (Taylor, 2011) confirmou que o TOC de início precoce tem maior probabilidade de ocorrer em homens e de estar associado com maior gravidade do TOC globalmente. Tem maior prevalência do TOC estar associado com tiques e com outros transtornos do espectro obsessivo-compulsivo, além de também de estar associado com maior prevalência de TOC em parentes de primeiro grau.

Enquanto a literatura tem dado grande importância ao TOC de início precoce, existe uma carência de estudos em pacientes que apresentam TOC pela primeira vez em estágios mais avançados da vida. Apesar do TOC de início tardio ser frequentemente associado a lesões cerebrais (Frydman et al., 2010), levando alguns autores a sugerir a investigação de organicidade subjacente sempre que o TOC surgir depois de 40 anos

de idade (Koran, 1999), casos de TOC aparecendo em idades mais avançadas sem nenhuma evidência de lesão cerebral subjacente podem ser comuns.

Não está claro se o TOC com idade de início mais tardio estaria associado a características específicas. Grant et al (Grant et al., 2007), em um estudo controlado, relataram que indivíduos que tiveram abertura do quadro de TOC com 30 anos ou mais (11,3% da sua amostra) apresentaram menor gravidade do transtorno, incluindo menor duração da doença antes do tratamento, obsessões mais suaves e menor frequência de obsessões de contaminação, religião ou somática. Não houve diferença em relação a presença de comorbidades, insight, sintomas depressivos, qualidade de vida e funcionamento social entre o grupo de início precoce e o tardio.

Conforme já mencionado novos estudos com foco no TOC de início tardio são necessários. Nesse sentido, conduzimos o estudo "Late-onset obsessive-compulsive disorder: risk factors and correlates" publicado no Journal of Psychiatric Research, no qual realizamos uma análise multinível investigando possíveis aspectos/fatores de risco associados ao desenvolvimento do TOC após os 40 anos de idade.

3 - Transtorno Obsessivo-Compulsivo e Transtornos Relacionados

Os primeiros relatos que temos de TOC no mundo ocidental data da idade média e, desde então, já foi classificado de diversas formas da psicose à neurose. Não é novidade a discussão se o TOC é um transtorno das emoções, cognição e/ ou vontade (Berrios, 1989). Na primeira edição do Manual Diagnóstico e Estatístico de Transtorno Mentais (DSM) o TOC foi classificado como uma neurose, em seguida, porém, nas versões posteriores foi reclassificado como transtorno de ansiedade e recentemente no DSM 5 foi inserido em um novo capítulo com o título de transtorno obsessivo-compulsivo e transtornos relacionados.

A controvérsia na classificação do TOC, portanto não é recente. Na verdade, enquanto a edição anterior do DSM (4ª edição) o classificava como transtorno de ansiedade, o Código Internacional de Doenças (CID), em sua 10ª edição, o classifica junto aos "transtornos neuróticos, relacionados ao estresse e somatoformes". O TOC parece se diferenciar dos transtornos de ansiedade por apresentar hiperatividade e hiperresponsividade no circuito fronto-estriado e resposta atenuada da amígdala a ameaças não relacionadas às obsessões. Isto pode ser um indicativo do TOC mais como um transtorno de déficits processuais implícitos e cognições intrusivas negativas do que um transtorno de ansiedade per se (Stein et al., 2010).

Diversos argumentos e inúmeras discussões foram levantadas a cerca dessa nova classificação. Os principais motivos para os transtornos deste novo capítulo terem sido agrupados são: pensamentos e comportamentos repetitivos e falha na inibição comportamental; sobreposição na idade de início, comorbidade e carga familiar; sobreposição na disfunções de circuitos cerebrais e neurotransmissores; e perfis de resposta ao tratamento semelhantes (Fineberg et al., 2010). Por outro lado, cabe ressaltar que diversas críticas foram formuladas a essa nova classificação, embora não seja o objetivo deste trabalho essa discussão (Abramowitz and Jacoby, 2015).

O capítulo de transtorno obsessivo-compulsivo e transtornos relacionados engloba dois novos transtornos, o transtorno de acumulação e o transtorno de escoriação (skin-picking). Também faz parte deste capítulo um transtorno antes classificado

como somatoforme, o transtorno dismórfico corporal e um anteriormente classificado como transtorno de controle dos impulsos, a tricotilomania (transtorno de arrancar o cabelo). A síndorme de referência olfatória (SRO) foi incluída como outro transtorno obsessivo-compulsivo e transtorno relacionado especificado. Apesar de evidências de similaridades em diversos aspectos, a síndrome de tourrete não entrou nesse capítulo e foi classificada como transtorno do neurodesenvolvimento (APA, 2013).

O transtorno dismórfico corporal tem uma prevalência durante a vida na comunidade de 0,7 a 2,4% e tem como principal sintoma a preocupação com a percepção de um ou mais defeitos ou falhas na aparência física não observáveis ou leves demais para os outros. O sujeito se sente compelido a realizar comportamentos repetitivos, como olhar no espelho, ou atos mentais excessivos, como comparar-se com outra pessoa, em resposta às preocupações. Há um tipo de transtorno dimórfico corporal chamado dismorfia muscular, em que o sujeito tem a crença que sua estrutura corporal é muito pequena e insuficientemente musculosa (APA, 2013).

Não temos ainda estudos epidemiológicos representativos no transtorno de acumulação, já que até recentemente era considerado um sintoma do TOC ou do transtorno de personalidade obsessivo-compulsivo. Pesquisas comunitárias estimam que a prevalência seja de 2 a 6% com predominância no sexo masculino, porém em amostras clínicas há predominância feminina. Nesse transtorno o sujeito tem dificuldade persistente de descartar ou de se desfazer de objetos, independente do seu valor real. Há convicção da necessidade de conservá-los e sofrimento com o seu descarte. Os objetos acumulados bloqueiam e congestionam áreas até o ponto que estas não podem mais ser utilizadas. Na maioria dos portadores há aquisição excessiva através de compra ou roubo de itens não necessários ou sem espaço disponíveis para os mesmos (APA, 2013).

A tricotilomania (transtorno de arrancar cabelos) tem prevalência de 1 a 2 % em 1 ano em adultos e adolescentes, sendo o gênero feminino mais afetado que o masculino, em uma razão 10:1. Em crianças ambos os gêneros são atingidos igualmente. É caracterizado por comportamento repetitivo de arrancar os próprios cabelos gerando perda de cabelo e tentativas repetidas de reduzir ou parar de arrancá-los, resultando em angustia ou prejuízo no funcionamento (APA, 2013).

O transtorno de escoriação (skin-picking) é caracterizado por cutucar ou beliscar a própria pele de forma repetida ou compulsiva gerando lesões cutâneas. Há tentativas repetidas de parar com o comportamento sem sucesso, gerando sintomas depressivos, imagem comporal negativa, evitação social e saúde debilitada. A prevalência na população em geral é de 1,4% em adultos, sendo que mais de três quarto dos acometidos são do sexo feminino (APA, 2013).

Dentre a categoria Outros Transtorno Obsessivo-Compulsivo e Transtornos Relacionados, podemos destacar a síndrome de referência olfatória. Neste transtorno o indivíduo tem preocupação exacerbada com a crença de exalar um odor ruim que não é perceptível por outras pessoas. O indivíduo pode tomar diversos banhos, escovar o dente diversas vezes, usar perfume em excesso ou evitar situações sociais, podendo ficar restrito em sua residência. Não há dados na literatura sobre sua prevalência. São encontrados em clínicas dermatológicas ou odontológicas com mais frequência do que em serviços de saúde mental (Begum and McKenna, 2010; Feusner et al., 2010).

Dados em relação à comorbidade dos transtornos do espectro obsessivo-compulsivo encontram-se de forma não sistematizada na literatura. No capítulo “Comorbidity in Obsessive-Compulsive and Related Disorders” do volume II do livro “The Wiley Handbook of Obsessive Compulsive Disorders” foi realizada uma revisão acerca da comorbidade dos transtornos do espectro obsessivo-compulsivo, incluindo síndrome de tourrete e síndrome de refêrencia olfatória.

4 - Diagnóstico

Na psiquiatria não há, até o momento, nenhum tipo de exame laboratorial que nos possibilite confirmação de determinado diagnóstico. O diagnóstico é realizado pelo clínico através da entrevista clínica e do exame psicopatológico. Exames são realizados para excluir alguma doença clínica ou neurológica. Os manuais diagnósticos como o DSM e o CID, existem para uniformizar a classificação diagnóstica nas diferentes partes do mundo. O clínico deve usá-los para avaliar se o sujeito preenche os critérios diagnósticos descritos. No quadro 1 encontram-se os critérios diagnósticos do TOC conforme o DSM e no quadro 2 conforme o CID.

Quadro 1 - Critérios diagnósticos do TOC de acordo com DSM 5

A. Presença de obsessões, compulsões ou ambas:
Obsessões são definidas por (1) e (2):
1. Pensamentos, impulsos ou imagens recorrentes e persistentes que, em algum momento durante a perturbação, são experimentados como intrusivos e indesejados e que, na maioria dos indivíduos, causam acentuada ansiedade ou sofrimento.
2. O indivíduo tenta ignorar ou suprimir tais pensamentos, impulsos ou imagens ou neutralizá-los com algum outro pensamento ou ação.
As compulsões são definidas por (1) e (2):
1. Comportamentos repetitivos (p. ex., lavar as mãos, organizar, verificar) ou atos mentais (p. ex., orar, contar ou repetir palavras em silêncio) que o indivíduo se sente compelido a executar em resposta a uma obsessão ou de acordo com regras que devem ser rigidamente aplicadas.
2. Os comportamentos ou os atos mentais visam prevenir ou reduzir a ansiedade ou o sofrimento ou evitar algum evento ou situação temida; entretanto, esses comportamentos ou atos mentais não têm uma conexão realista com o que visam neutralizar ou evitar ou são claramente excessivos.
Nota: Crianças pequenas podem não ser capazes de enunciar os objetivos desses comportamentos ou atos mentais.
B. As obsessões ou compulsões tomam tempo (p. ex., tomam mais de uma hora por dia) ou causam sofrimento clinicamente significativo ou prejuízo no funcionamento social, profissional ou em outras áreas importantes da vida do indivíduo.
C. Os sintomas obsessivo-compulsivos não se devem aos efeitos fisiológicos de uma substância (p. ex., droga de abuso, medicamento) **ou a outra condição médica.**
D. A perturbação não é mais bem explicada pelos sintomas de outro transtorno mental (p. ex., preocupações excessivas, como no transtorno de ansiedade generalizada; preocupação com a aparência, como no transtorno dismórfico corporal; dificuldade de descartar ou se desfazer de pertences, como no transtorno de acumulação; arrancar os cabelos, como na tricotilomania [transtorno de arrancar o cabelo]; beliscar a pele, como no transtorno de escoriação [skin-picking]; estereotipias, como no transtorno de movimento estereotipado; comportamento alimentar ritualizado, como nos transtornos alimentares; preocupação com substâncias ou jogo, como nos transtornos relacionados a substâncias e transtornos aditivos; preocupação com ter uma doença, como no transtorno de ansiedade de doença; impulsos ou fantasias sexuais, como nos transtornos parafílicos; impulsos, como nos transtornos disruptivos, do controle de impulsos e da conduta; ruminações de culpa, como no transtorno depressivo maior; inserção de pensamento ou preocupações delirantes, como nos transtornos do espectro da esquizofrenia e outros transtornos psicóticos; ou padrões repetitivos de comportamento, como no transtorno do espectro autista).
Especificar se:
Com insight bom ou razoável: O indivíduo reconhece que as crenças do transtorno obsessivo-compulsivo são definitiva ou provavelmente não verdadeiras ou que podem ou não ser verdadeiras.
Com insight pobre: O indivíduo acredita que as crenças do transtorno obsessivo-compulsivo são

provavelmente verdadeiras.
Com insight ausente/crenças delirantes: O indivíduo está completamente convencido de que as crenças do transtorno obsessivo-compulsivo são verdadeiras.
Especificar se:
Relacionado a tique: O indivíduo tem história atual ou passada de um transtorno de tique.

Quadro 2 - Critérios para diagnóstico do TOC de acordo com a Classificação Internacional das Doenças 10a revisão (CID-10):

A. Compulsões ou obsessões (ou ambas) estão presentes na maioria dos dias, por um período de pelo menos duas semanas.

B. Obsessões (pensamentos ideias, imagens) e compulsões (atos) compartilham os seguintes aspectos os quais devem estar presentes:

1) São reconhecidas como originando-se da mente do paciente e não impostas por pessoas ou influências externas.

2) São repetitivas e desagradáveis e pelo menos uma obsessão ou compulsão reconhecida como excessiva e irracional deve estar presente.

3) O paciente tenta resistir a elas, (mas a resistência a obsessões ou compulsões de longa duração pode ser mínima mesmo que minimamente). Pelo menos uma obsessão ou compulsão à qual se resiste sem êxito deve estar presente.

4) A vivência do pensamento obsessivo ou a realização do ato compulsivo não é prazerosa em si mesma (isto deve ser distinguido do alívio temporário de tensão ou ansiedade).

C. As obsessões ou compulsões causam angústia ou interferem com o funcionamento social ou individual do paciente, usualmente pela perda de tempo.

D. As obsessões e compulsões não são o resultado de outros transtornos mentais tais como esquizofrenia e transtornos relacionados ou transtornos do humor.

Nesta última edição do DSM algumas pequenas modificações foram feitas nos critérios diagnósticos de TOC. Tanto o conceito de obsessão como o de compulsão foram clarificados e simplificados através, por exemplo, da substituição da palavra "impróprio" por "indesejável. O antigo critério B em que era necessário o reconhecimento das obsessões como excessivas e não razoáveis foi abolido, com a justificativa de ser um critério subjetivo e difícil de operacionalizar. No texto explicativo consta de forma mais clara a palavra evitação e sua função semelhante a de uma compulsão, que as obsessões e compulsões usualmente não são agradáveis e as principais dimensões de sintomas. O critério C de significância clínica foi reescrito e passou para B e o critério D em que se descrevem os diagnósticos diferenciais também foi reescrito, além de ter sido ampliado. Conforme já descrito, foi incluído

um subtipo de TOC relacionado a tiques e foram revisados os especificadores de insight que podem variar de “bom” até “ausente” (Leckman et al., 2010).

A CID está no momento passando por sua 11ª revisão, ainda sem data para lançamento. Nessa revisão está sendo proposto, seguindo a mesma lógica do DSM, o agrupamento do transtorno obsessivo-compulsivo e transtornos relacionados. Nesse grupo além do TOC é proposto que o transtorno hipocondríaco e o transtorno dismórfico corporal, no momento também classificado no grupo de transtornos neuróticos, relacionados ao estresse e somatoformes, façam parte. A tricotilomania deverá sair do grupo atual de transtornos dos hábitos e impulsos para fazer parte, junto com o novo transtorno de escoriação (skin-pickin), de um subgrupo de transtornos de comportamento repetitivo focado para o corpo. Outros dois novos transtornos são propostos, o transtorno de acumulação e a síndrome de referência olfatória (Stein et al., 2016).

Existem algumas mudanças propostas para o diagnóstico de TOC na CID 11 que serão enumeradas aqui: haverá o reconhecimento de que tanto um fenômeno cognitivo como sensorial pode preceder um comportamento compulsivo (Ferrao et al., 2012; Shavitt et al., 2014), e apesar das obsessões ainda serem descritas como comumente associadas com ansiedade, essas também podem estar associadas com sensação de nojo exacerbado (Husted et al., 2006a; Olatunji et al., 2017), sensação angustiante de “incompletude” ou a uma inquietação até as coisas parecerem estar da “maneira certa” (“*just right*”) (Ferrao et al., 2012). As compulsões não serão descritas como comportamentos repetitivos estereotipados, mas como hábitos repetitivos para não serem confundidos com comportamentos estereotipados presentes por exemplo no autismo e para incluir os rituais mentais (Foa et al., 1995).

Não haverá especificação de um tempo mínimo necessário de sintomas para o diagnóstico, já que não há dados na literatura que embasem esse critério. Porém, será solicitado cuidado no diagnóstico de sujeitos com menos de 1 mês de doença e exclusão de outras etiologias em casos de início abrupto, principalmente em crianças (Stein et al., 2016). Será descrita uma relação funcional entre obsessões e compulsões, para facilitar os clínicos no diagnóstico diferencial com transtornos com sintomas puramente obsessivos (como ruminação depressiva ou preocupações excessivas no

transtorno de ansiedade generalizada) assim como de transtornos que cursam com comportamentos repetitivos (como tricotilomania ou autismo) (Stein et al., 2016).

Os subtipos que existem na CID 10 de TOC com predominância de ideias ou de ruminações obsessivas, TOC com predominância de comportamentos compulsivos (rituais obsessivos) e TOC forma mista, com ideias obsessivas e comportamentos compulsivos serão eliminados na CID 11. Estes subtipos não encontram respaldo nas pesquisas atuais, não possuem valor preditivo na resposta terapêutica e a maioria dos pacientes apresentam tanto obsessões como compulsões (Foa et al., 1995; Shavitt et al., 2014). Será eliminada a instrução de que em caso de depressão maior associada, o diagnóstico de TOC não pode ser realizado (Stein et al., 2016). Além disso, será autorizado o diagnóstico comórbido de TOC com transtorno de tiques. Haverá um sistema de "múltipla parentalidade" que permite outras categorias diagnósticas encontradas em diferentes capítulos tenham referências cruzadas quando legitimamente possam pertencer a dois capítulos, como no caso da síndrome de Tourrete (Stein et al., 2016).

Apesar do aprimoramento e modernização dos manuais clínicos diagnósticos, a busca pela identificação de um biomarcador segue relevante. Biomarcador é definido como uma característica que pode ser objetivamente medida como um indicador de um processo biológico normal, processos patológicos ou resposta farmacológica a uma intervenção terapêutica (Group, 2001). Por mais que na maioria dos casos um clinico bem treinado seja capaz de realizar o diagnóstico de TOC, ter um marcador seria uma forma de confirmação diagnóstica, além de contribuir para melhor entendimento do transtorno para aprimorarmos a terapêutica. O trabalho seguinte busca melhor compreender este tema, o artigo "Can Neuroimaging Provide Reliable Biomarkers For Obsessive-Compulsive Disorder? A Narrative Review" publicado na Current Psychiatry Reports é uma revisão qualitativa da presente literatura de possíveis neurobiomarcadores no TOC.

5 - Espectro Compulsivo-Impulsivo

A elaboração da nova classificação do TOC no DSM e no CID traz à tona a discussão de um espectro compulsivo-impulsivo. Diversos autores sugerem um *continuum* impulsivo-compulsivo que englobaria os transtorno obsessivo-compulsivo e transtornos relacionados, o transtorno de personalidade obsessivo-compulsivo, transtorno de controle dos impulsos, transtorno de déficit de atenção e hiperatividade e até mesmo transtornos de abuso de substância e transtornos alimentares (Stein et al., 2016). Esse assunto não é simplesmente uma questão classificatória, já que pode implicar em mudanças na forma terapêutica atual e em novas propostas.

Há alguns anos a visão da compulsividade e impulsividade como constructos diametralmente opostos (aversão ao risco X busca por recompensa) vem sendo questionado e a hipótese de que na verdade seriam dimensões ortogonais ganha cada vez mais espaço na literatura (Grant et al., 2010; Hollander, 1993; Hollander and Wong, 1995). Postula-se que esses dois constructos podem mesmo coexistir em um mesmo paciente que pode, a um só tempo, ser impulsivo e com TOC (Fontenelle et al., 2005). Evidências de traços de impulsividade no TOC (Chamberlain et al., 2006; Ettelt et al., 2007; Penadés et al., 2007) e de características compulsivas na adição e outros transtornos de controle dos impulsos (Grant and Potenza, 2006) corroboram a hipótese que impulsividade e compulsividade compartilham mecanismos, tanto no que concerne aspectos psicopatológicos como neurobiológicos.

Existem diversas definições na literatura para estes dois constructos, o que traduz a complexidade do tema. Compulsividade pode ser definida como "a tendência de realizar atos repetitivos de uma forma habitual/estereotipada na tentativa de prevenir consequências desfavoráveis" (Fineberg et al., 2010). Já impulsividade é melhor definida como "a predisposição à reações rápidas, não planejadas a estímulos internos ou externos sem considerar as consequências negativas dessas reações ao próprio indivíduo impulsivo ou à outras pessoas" (Moeller et al., 2001).

Comportamentos impulsivos e compulsivos podem ser o resultados de falhas do controle cortical dos circuitos fronto-estriatais com substratos neurais sobrepostos e

distintos. Enquanto a impulsividade envolve os circuitos ventrais, a compulsividade envolve os dorsais. Considerando esses fatos, um modelo comportamental de adição foi proposto para o TOC, no qual a impulsividade se tornaria mais proeminente com a progressão, gravidade e cronicidade do transtorno. Os sintomas se tornariam mais ego-sintônicos e menos ego-distônicos com o passar do tempo e os pacientes poderiam apresentar "compulsões impulsivas" (Fineberg et al., 2010; Fontenelle et al., 2011; Grant et al., 2010).

Devido à grande controvérsia que esse assunto levanta, realizamos um estudo investigando a impulsividade, em seus diversos aspectos, em um grupo de pacientes com TOC com o título "Subjective and objective impulsivity in obsessive-compulsive disorder" submetido no Journal of Behavioral Addiction.

6 - Neurociência social do TOC

Neurociência social é um novo campo interdisciplinar dedicado a entender como sistemas biológicos implementam processos sociais e comportamentais. Surgiu no início dos anos 1990 como um campo interdisciplinar utilizando conceitos e métodos biológicos para informar e refinar teorias do comportamento social, além de utilizar dados e constructos sociais e comportamentais para também informar e refinar teorias da função e organização neural (Cacioppo et al., 2007; Zahn et al., 2012). Trata-se de um campo que cresce cada vez mais, sugerindo que a conexão entre neurociência e ciências sociais é de fato prática e indica um potencial para linguagem científica comum que pode estabelecer caminhos necessários para conectar os termos teóricos destas ciências.

O famoso caso de Phineas Gage que apresentou alteração de comportamento após um acidente em que uma barra de ferro atravessou os córtex orbitofontal e ventromedial em 1848 (Harlow, 1868), levantou a importância de delinearmos os componentes do comportamento social. Esta compreensão pode nos levar, por sua vez, a entendermos comportamentos sociais funcionais e disfuncionais, sua relação com a psicopatologia, as bases neurais do processo destes componentes comportamentais e diáteses específicas para doenças mentais.

Nosso entendimento das bases neurais do comportamento social humano é ainda muito limitado. Uma forma de entendimento seria utilizarmos a pesquisa básica para estabelecer modelos normativos de mecanismos que apoiam o funcionamento social em indivíduos saudáveis. Em seguida, esses modelos poderiam prover bases conceituais e metodológicas para explicar como o comportamento social se desmembra em diversas doenças clínicas (Cacioppo et al., 2007). Porém a maior parte do entendimento é baseado na observação clínica, testagem neuropsicológica e mais recentemente ressonância magnética cerebral funcional de pacientes com lesões cerebrais (Zahn et al., 2012).

A neuroimagem tem um papel fundamental no estudo de habilidades sociais humanas, que envolve processos cognitivos elevados, devido a dificuldade de realizá-los em

animais (Zahn et al., 2012). Ao mesmo tempo, estudos com animais são de extrema importância para detalhamento de modelos moleculares e das bases subcorticais nas formas simples de aprendizado emocional, afiliação e conexão entre pares (Cacioppo et al., 2007). Uma compreensão mais completa do comportamento social humano requer análises de múltiplos níveis (contexto individual, familiar e da sociedade) que estimulam as pessoas a inibir ou exibir certos comportamentos, pensamentos ou emoções nos níveis genético, molecular e sistêmico (Moll et al., 2005b).

O comportamento social pode ser definido como um comportamento que envolve mais de uma pessoa ou um comportamento que tem consequências para mais de uma pessoa (Zahn et al., 2012). Podemos dividi-lo em quatro amplas subcategorias: auto-percepção, auto-regulação, percepção interpessoal e processo de grupo (Cacioppo et al., 2007). A auto-percepção tem papel essencial, visto que geralmente uma visão positiva sobre si mesmo é de extrema importância para a saúde mental do indivíduo. Além disso, sua disfunção gera implicações importantes na psicopatologia. Classicamente doenças como a esquizofrenia e depressão cursam com distúrbio na auto-percepção ou no agenciamento e no processamento de informações relevantes sobre si, respectivamente (Cacioppo et al., 2007).

Nesse contexto, a auto-regulação é considerada como um controle de ordem superior para processos de ordem inferiores responsáveis pelo planejamento e execução dos comportamentos. Não é restrito a processos de função executiva, mas também engloba o controle emocional (Cacioppo et al., 2007). Falhas na auto-regulação estão implicadas no controle dos impulsos, na esquizofrenia, autismo, transtorno de déficit atenção e hiperatividade, síndrome de Tourrete e TOC. No TOC, por exemplo, se discute uma falha no processo de comparar o status atual com a expectativa de alcançar um objetivo (Johannes et al., 2001). A habilidade da auto-regulação emocional parece ser essencial para o funcionamento social, tendo em vista que falhas na auto-regulação de emoções negativas estão presentes na maioria dos transtornos enumerados pelo DSM (Cacioppo et al., 2007).

A percepção interpessoal e o processo de grupo são de tamanha importância que estudos mostram que déficits no relacionamento social em geral é associado com maior morbidade e mortalidade (House et al., 1988). A habilidade de entender,

interagir e conectar com outros sujeitos é essencial para o bem-estar tanto físico como mental. No transtorno de personalidade borderline e na fobia social, por exemplo há uma tendência de se perceber erroneamente a intenção real da outra pessoa e no autismo há inabilidade nesta percepção (Cacioppo et al., 2007). Estudos de neuroimagem vêm com a promessa de ajudar a elucidar as bases neurais do comportamento social em sujeitos sadios e nos inúmeros transtornos psiquiátricos existentes (Moll et al., 2011).

O comportamento social humano é influenciado pela habilidade de saber o que é moralmente "certo" e "errado" (Zahn et al., 2012), emoções morais, que na realidade desempenham papel fundamental influenciando nosso dia a dia (Moll et al., 2007). Ainda não temos uma teoria neurocientífica estável sobre a moral. Nos referimos à moralidade como o consenso de normas, valores e costumes de um grupo social que influenciam a tendência deste grupo a se comportar de uma determinada maneira, uma visão que não assume a existência de valores morais absolutos (Moll et al., 2005b). Nosso cérebro intuitivamente concebe o mundo de maneira moral, nos dotando, em nossa maioria, com um sentido intuitivo de justiça, preocupação pelo próximo e cumprimento de normas (Moll et al., 2007).

Apesar dos conceitos de emoção, sentimento, afeto, humor serem frequentemente usados na literatura neuropsiquiátrica, há uma diversidade imensa nos construtos usados tanto por clínicos quanto por psicólogos e neurocientistas. A emoção tipicamente tem um componente expressivo, ela se diferencia do afeto, que é mais direto e simples (negativo ou positivo), por envolver um processo de avaliação mais complexo, e do humor por apresentar duração mais curta (Rozin, 2003). Todas emoções são respostas da nossa percepção a mudanças, ameaças e oportunidades no mundo. Na maioria das vezes a própria pessoa é diretamente afetada por esses eventos, por exemplo quando alguma coisa boa acontece conosco ficamos alegres (Rozin, 2003).

Da perspectiva da psicopatologia, autores clássicos (Schneider, 1959) observaram que emoções ou sentimentos são frequentemente baseados em "objetos" que as pessoas estimam ou têm como referência, as pessoas podem amar ou odiar algo ou alguém, incluindo elas mesmas. Nas primeiras tentativas de sistematizar as emoções foram

divididas em valências positivas e negativas ambas referindo-se potencialmente ao próprio, como culpa e orgulho ou a outras pessoas e objetos, como nojo e carinho (Fontenelle et al., 2015).

Quando as emoções estão relacionadas aos interesses ou ao bem-estar da sociedade como um todo ou ao menos a outras pessoas que não o próprio, elas são consideradas emoções morais, ainda que provavelmente haja benefícios indiretos para a própria pessoa (Haidt, 2003). Ou seja, são um grupo de experiências afetivas que promovem cooperação, coesão e reorganização do grupo (Fontenelle et al., 2015).

Conforme já mencionado acima, as emoções morais têm um papel central na condução do nosso comportamento social no dia a dia (Moll et al., 2007) e são culturalmente universais independente da diversidade cultural de diferentes grupos sociais (Fessler, 1999). São consideradas emoções morais culpa, nojo, medo, raiva, indignação, vergonha, arrependimento, gratidão, orgulho, constrangimento, inveja, pena, desprezo e ciúmes (Haidt, 2003; Moll et al., 2007).

Considera-se, ainda, que as emoções morais emergem como representações neurais dependentes da coativação de regiões cerebrais que simbolizam a percepção de estímulos sociais (junção temporo-parietal e outras regiões corticais posteriores), aprendizado social conceitual (principalmente córtex temporal anterior), aprendizado de um evento sequencial abstrato (setores anteriores, mediais e laterais do córtex pré-frontal) e estados emocionais básicos (incluindo estruturas subcorticais como a base do prosencéfalo e hipotálamo) (Fontenelle et al., 2015; Moll et al., 2005a; 2008).

Estados emocionais negativos como raiva, confusão, depressão, fadiga e tensão foram correlacionados com maior gravidade de sintomas obsessivo-compulsivos em uma amostra não clínica (Spinella, 2005). Além disso, observamos na literatura que o TOC está associado com diversos transtornos que possuem como característica principal experiências emocionais aplainadas, como o autismo (Ivarsson and Melin, 2008), transtorno de personalidade esquizotípico (Poyurovsky et al., 2008) e esquizofrenia (Devi et al., 2015).

Existem dados na literatura sugerindo que o TOC estaria associado a algumas características como problemas na forma de como se experiência
(Lawrence et al., 2007; Moscovitch et al., 2008; Starcke et al., 2009; Whiteside and Abramowitz, 2005), avalia (Calamari et al., 2008; Calkins et al., 2013), expressa (Bersani et al., 2012; Pasquini et al., 2010) e reconhece (Aigner et al., 2007; Bersani et al., 2012; Corcoran et al., 2008; Montagne et al., 2008) diferentes tipos de emoções.

Observamos um número crescente de estudos de neuroimagem com o objetivo de identificar correlatos neurais da percepção e experiência de diferentes tipos de emoções no TOC, incluindo nojo (Berle and Phillips, 2006; Britton et al., 2010; Husted et al., 2006b; Lawrence et al., 2007; Weygandt et al., 2012), medo (Britton et al., 2010; Cannistraro et al., 2004; Lawrence et al., 2007; Shapira et al., 2003), alegria (Britton et al., 2010; Cannistraro et al., 2004; Weygandt et al., 2012), raiva (Whiteside and Abramowitz, 2005), culpa (Basile et al., 2013; Hennig-Fast et al., 2015) e vergonha (Hennig-Fast et al., 2015). Porém, os resultados são ainda contraditórios. Por exemplo, não está claro se o medo relacionado ao TOC está relacionado com hipo- (Britton et al., 2010; Cannistraro et al., 2004), hiper- (Simon et al., 2014) ou normo- (Lawrence et al., 2007) reatividade da amigdala; ou se a experiência de nojo no TOC está associada com hiper- (Shapira et al., 2003) ou hipo- (Gilbert et al., 2009) responsividade da insula e circuitos relacionados. A inconsistência desses achados são, provavelmente, reflexo da heterogeneidade e tamanho das amostras, diferentes status de medicação e divergência na estratégica de foco na provocação de sintomas do que da emoção em si, o uso de estímulos adaptados individualmente ou mais amplos, e o uso de estímulos mais curtos ou mais longos para provocação de sintomas (Britton et al., 2010; Gilbert et al., 2009; Schienle et al., 2005; Simon et al., 2014; van den Heuvel et al., 2004).

Conforme colocado por Keltner and Kring, 1998: "... tendo em vista a prevalente associação entre distúrbios emocionais e a psicopatologia, pesquisas básicas sobre as emoções e interação social fornecem estrutura conceitual para considerar possíveis causas e consequências de distúrbios emocionais assim como potenciais intervenções". Tendo isso em mente, talvez um estudo mais profundo das emoções morais possa nos ajudar a entender sintomas e disfunções comportamentais presentes

no TOC, com este objetivo conduzimos o estudo “Decoding Moral Emotions in Obsessive-Compulsive Disorder” submetido para a revista Neuroimage: Clinical.

7- Artigos/Capítulo

Late-onset obsessive-compulsive disorder: risk factors and correlates

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Abstract

Background: While a great amount of attention has been paid to early-onset obsessive-compulsive disorder (OCD), there is a dearth of studies on patients showing OCD for the first time at later stages of life. In this study, we aimed at determining possible risk factors/ correlates for OCD onset at or after age 40, here termed late-onset OCD. **Method:** A series of models including several potential variables associated with late onset OCD were tested using a monolayer neural network. To this regard, data from the Brazilian Research Consortium of Obsessive-Compulsive Spectrum Disorders (CTOC) (n= 1001) was employed. For the purposes of this study, we considered a diagnosis of late onset OCD to be present whenever distress and interference associated with OCD symptoms emerged at or after age 40. Different nested models were compared through the Akaike Criteria keeping the variables with p value ≤ 0.05. **Results**: Late-onset OCD occurred in 8.6% of the sample. A model including female sex, a history of chronic (> 10 years) subclinical obsessive-compulsive symptoms, the co-occurrence of posttraumatic stress disorder (PTSD) after age 40, and a history of recent pregnancy in self or significant others was able to explain a sizeable proportion of late-onset OCD. The general performance of this model, represented by the Maximum Likelihood R2, was 29.4%. **Conclusion:** Our results suggest that late-onset OCD is more likely to occur in females, in individuals with long periods of subclinical obsessive-compulsive symptoms, and in association with a major traumatic event occurring after age 40 and a history of recent pregnancy in self or in significant others.

Key words: obsessive-compulsive disorder, clinical course, onset, late-onset, phenotype.

Introduction

Obsessive-compulsive disorder (OCD) is characterized by intrusive and distressing images, thoughts or urges (obsessions) and/or repetitive mental or motor acts aimed at reducing the anxiety or performed according to certain rules (compulsions). Epidemiological studies employing the Composite International Diagnostic Interview (CIDI) suggest that OCD is a frequent condition, with 1-month prevalence ranging from 0.3 to up to 3.1% (Fontenelle and Hasler, 2008). Most patients with OCD exhibit an onset of symptoms during adolescence or childhood (Fontenelle and Hasler, 2008). A recent meta-analysis (Taylor, 2011) confirmed the long held view that early-onset OCD is associated with male sex, greater OCD global severity, higher prevalence of most types of OC symptoms and of OCD in first-degree relatives, and comorbidity with tics and other obsessive-compulsive spectrum disorders.

While a great amount of attention has been paid to early-onset OCD, there is a dearth of studies on patients showing OCD for the first time at later stages of life. In fact, much of what is known about late-onset OCD is still based on single case reports and small case series (Frydman et al., 2010). Although late-onset OCD has been commonly associated with coarse brain injury (Frydman et al., 2010), prompting some to suggest that one should always investigate underlying organicity when OCD presents after age 40 (Koran, 1999), cases of OCD firstly appearing on later stages of the life cycle without any evidence of underlying brain lesions are probably more common.

To the best of our knowledge, only one systematic, controlled study tried to delineate the phenotype of patients presenting late-onset OCD without evidence of brain injury (Grant et al., 2007). In this study, Grant et al reported that individuals who had OCD onset at or after age 30 years (11.3% of their sample) displayed, overall, a less severe condition, including significantly shorter duration of illness before treatment, milder obsessions, and less frequent contamination, religious, or somatic obsessions. Of note, comorbidity, insight, depressive symptoms, quality of life, and social functioning did not differ between early and late-onset groups.

It is possible that OCD appearing at latter stages of life (e.g. not before age 40 years) would be associated with even more clear-cut features. Indeed, as of yet, there is no consensus on what should be termed ‘‘late-onset OCD,’’ with various researchers suggesting quite distinctive ages at onset for this condition (e.g., 30, 40, or even 50 years as cut-off points) (Frydman et al., 2010). One needs to consider that OCD developing after age 30 (Grant et al., 2007) may still include some forms of the disorder that are essentially identical to early-onset OCD, and that low cut-off ages related to OCD onset may potentially minimize differences between late-onset and early-onset illness. Likewise, it is not clear whether age of onset should be determined according to the beginning of the obsessive-compulsive symptoms (OCS) or when the level of clinical impairment warrants a diagnosis of OCD (Rosario-Campos et al., 2001). In the present study, we defined “age of onset” of OCD as the age when distress and interference were firstly associated with OCS.

In this study, we aimed at determining possible risk-factors/ correlates for OCD occurring at or after age 40, here termed late-onset OCD. Based on the available literature, we tested the performance of a series of statistical models (see figure 1) where female individuals (Fontenelle et al., 2002; Mathis et al., 2011; Torresan et al., 2009) with a family history of OCD (Albert et al., 2002; Roussos et al., 2003; Viswanath et al., 2011) and a personal history of subclinical obsessive-compulsive (OC) symptoms (Coles et al., 2011; Fullana et al., 2009; Roussos et al., 2003) would be at increased risk of developing late-onset OCD in the event of different environmental stressors (Murphy et al., 2010), such as birth and pregnancy (Forray et al., 2010), personal/family problems (Basile et al., 1996) and changes in interpersonal relationships (Tolin et al., 2010), infections (e.g. w/ group A β-hemolytic streptococcus) (Alvarenga et al., 2009), or exposure to drugs (e.g. atypical antipsychotics) (Ryu et al., 2011). We also investigated whether a major depressive episode (Gittleson, 1996a; 1996b; Quarantini et al., 2011) and severe psychological trauma, as portrayed by comorbid post-traumatic stress disorder (Fontenelle et al., 2011; Fontenelle et al., 2012; Moraes et al., 2008) (both occurring after age 40), could have any role in the development of late-onset OCD.

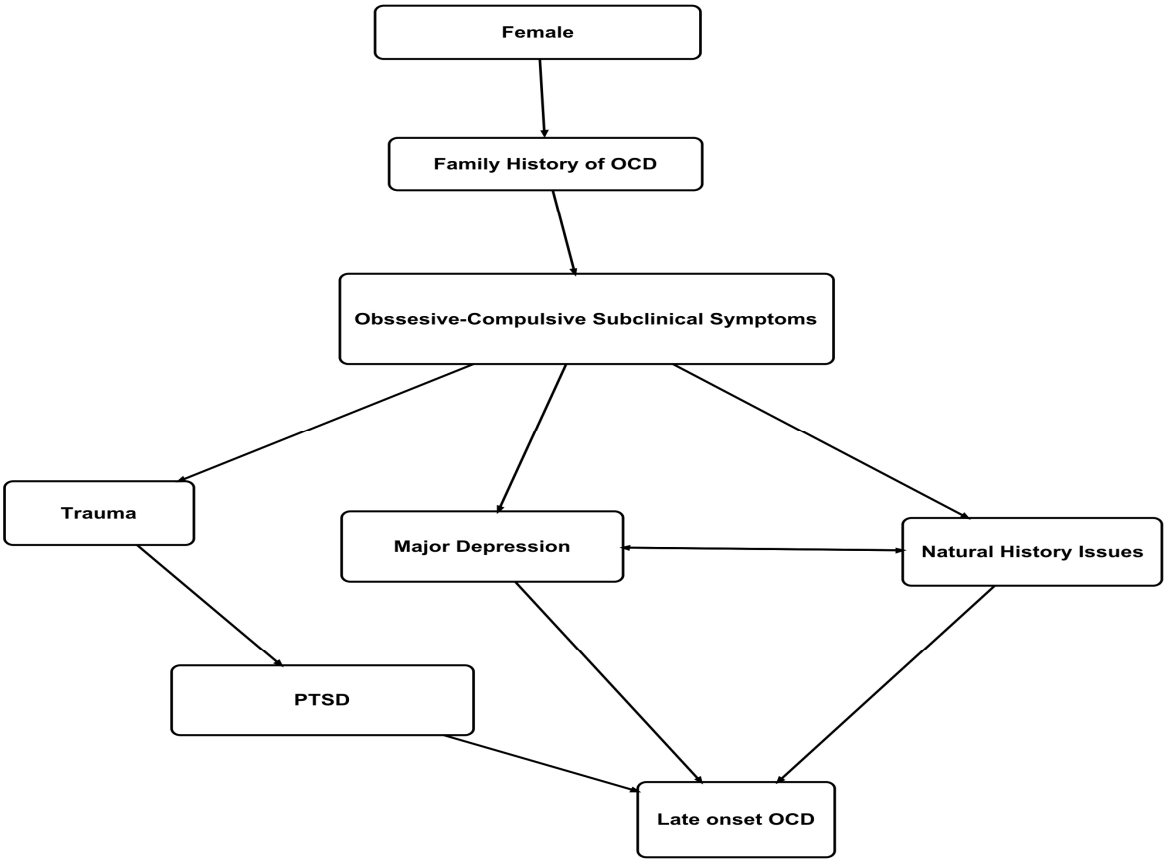

Figure 1 - Late onset- OCD risk factors and correlates algorithm

Method

Patients

Our sample was composed of 1001 OCD patients from the Brazilian Research Consortium on Obsessive-Compulsive Spectrum Disorders (CTOC). Patients were recruited from seven universities in six different Brazilian cities. All patients met DSM-IV criteria for OCD and were interviewed from August 2003 to August 2009 with the Structural Clinical Interview for DSM-IV Axis I disorders (SCID-I). Patients with cognitive disability, schizophrenia and OCD due to a general medical condition were excluded. All Research Ethics Committee from the University Hospitals involved approved this protocol. Participants signed a written informed consent after the procedures involved in our research protocol were fully explained (Miguel et al., 2008).

Instruments

A more detailed description of the recruitment of the patients, assessment instruments, implementation and method is available elsewhere (Miguel et al., 2008). Axis I disorders were diagnosed according to the Structured Clinical Interview for DSM-IV (SCID-I) (First et al., 1997). We employed the Yale OCD Natural History Questionnaire to access age at OCD onset and several life events and situations that may contribute to trigger, worsen or improve symptoms (Leckman et al., 2002, unpublished manuscript, translated into Portuguese by Rosário et al., 2002). Self-reported data on family history was indirectly obtained by interviewers using a series of screening questions.

For the purposes of this study, we considered the onset of OCD to have occurred at the age when distress and interference were firstly associated with OCS. Accordingly, OCD was classified into early-onset (onset before or at 16 years-old), regular-onset (onset after age 16 but before 40 years-old), and late-onset (onset at or after 40 years-old). Based on data provided by the Yale OCD Natural History Questionnaire, mode of OCD onset was classified into acute (if pre-OCD OCS lasted for less than 2 years) or protracted (if pre-OCD OCS lasted for more than 2 years). Chronic OCS were deemed to be present if lasting for at least 10 years preceding OCD onset. Pre-symptomatic life events/stressors were clustered into those related to (1) birth, (2) pregnancy, (3) personal or (4) family problems, (5) personal illness, (6) residence changing, (7) modification in cohabitants' behaviour, (8) love, intimate relationships; and marriage and (9) drug use. Co-occurring PTSD and MDD were considered to be of late onset if, as for OCD, appeared for the first time after or at age 40.

Although patients were also assessed with the Dimensional Yale-Brown Obsessive-Compulsive Scale (DY-BOCS) (Rosario-Campos et al., 2006), the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989), the Sensory Phenomena Scale (SPS) (Rosario-Campos et al., 2009), the Beck Depression and Anxiety Inventories (BDI and BAI, respectively) (Cunha, 2001) and the Brown Assessment of Beliefs Scale (BABS) (Eisen et al., 1998), patterns of response to these

scales were not included in our study, as we were unable to find data supporting their relationship to late-onset OCD.

Statistical analysis

All analyses were conducted with R-project version 2.15 (http://www.r-project.org/). A descriptive analysis of the variables was performed to compare participants with and without the outcome of interest (late-onset OCD). Continuous data were described as either medians and interquartile ranges or means and standard deviations and categorical data were reported as absolute and relative values. Kruskal-Wallis test was performed to compare continuous variables between groups. Pearson Chi square test was used to compare categorical variables and Fisher exact test was employed whenever any cell displayed less than five subjects.

A monolayer network was created with 3 denouement categories, i.e. early-onset ($\leq$ 16 years-old), regular-onset ($>$ 16 but $<$ 40 years-old), or late-onset OCD ($\geq$ 40 years-old). Gender, family history, mode of onset, life events, and co-occurring late-onset MDD or PTSD were entered in a series of nested models, which were compared through the Akaike Criteria (Akaike, 1969), keeping the variables with p value ≤ 0.05. From this initial/full model, we achieved a final one after again aligning and comparing different nested models through the Akaike Criteria, and also keeping the variables with $p \leq 0.05$, despite of the strengthens of the association. The McFadden and Maximum likelihood R2 were employed to evaluate the general performance of the final model.

Results

Descriptive Analysis

From the 1001 patients database only 983 were included in our analysis because 18 patients did not remember the age at which distress and interference related to OC symptoms started. From this sample, 8.6% (n= 85) reported displaying significant impairment at or after 40 years old (i.e. late-onset OCD), 22.5% before or at 16 years old (i.e. early-onset OCD) and 68.7% between 17 and 39 years old (i.e.regular OCD).

Comparisons between the three groups in terms of sociodemographic and clinical data, patterns of comorbidity, and aspects related to natural history are depicted in tables 1, 2 and 3, respectively.

Table 1: Sociodemographic and clinical features of obsessive-compulsive patients with late, early and regular onset of the disorder.

	Early-onset OCD n=222 (% or IQR)	Regular OCD n=676 (% or IQR)	Late-onset OCD n=85 (% or IQR)	Total n=983 (% or IQR)	Statistics	P value
Gender					Chi sq. (df = 2) = 16.2	< 0.001
Male	115 (51.8)	283 (41.8)	23 (27)	421 (42.8)		
Female	107 (48.2)	393 (58.1)	62 (72.9)	562 (57.2)		
Median age (in yrs)	26 (20-33.7)	33 (25-42)	52 (46-58)	32 (25-44)	Kruskal-Wallis test	< 0.001
Median age at onset (in yrs)	12 (10-13)	20 (17-26)	45 (41-50)	19 (15-27)	Kruskal-Wallis test	< 0.001
Marital status						
Married	54 (24.3)	264 (39.1)	51 (60)	369 (37.5)	Chi sq. (df = 2) = 35.48	<0.001
Cohabitation						
W/ parents	136 (62.1)	291 (44)	6 (7,5)	433 (45.1)	Chi sq. (df = 6) = 76.7	<0.001
W/ partner	49 (22.4)	259 (39.1)	46 (57.5)	354 (36.8)	Chi sq. (df = 6) = 76.7	<0.001
W/ parents or partner	207(94.5)	613 (92.6)	69 (86.3)	889 (92.5)	Chi sq. (df = 2) = 5.8	0.05
W/ out any of the above	12 (5.5)	49 (7.4)	11 (13.8)	72 (7.5)	Chi sq. (df = 6) = 76.7	<0.001
Economical productivity						
Economically active	83 (38.1)	358 (54.2)	31 (38.8)	472 (49.3)	Chi sq. (df = 2) = 21	<0.001
Children	43 (19.4)	270 (39.9)	68 (80)	381 (38.8)	Chi sq. (df = 2) = 92.79	<0.001
BABS total median score (IQR)	6 (2-11)	6(3.75-10)	6 (2-10)	6 (2-11)	Kruskal-Wallis test	0.616
Positive family history of OCS	120 (54)	333 (49.3)	43 (50.6)	496 (50.5)	Chi sq. (df = 2) = 1.5	0.5
Mode of onset of OCS						
Acute (< 2 years)	93 (43)	114 (17.3)	11 (13.7)	218 (22.8)	Chi sq. (df = 2) = 65.3	< 0.001
Protracted (> 2 years)	123 (56.9)	545 (82.7)	69 (86.2)	737 (77.2)	Chi sq. (df = 2) = 65.3	< 0.001
Chronic OCS (> 10 years)	2 (0.9)	292 (44.3)	65 (81.2)	359 (37.6)	Chi sq. (df = 2) = 201.4	< 0.001

OCS = Obsessive-Compulsive Symptoms; IQR = interquartile range

Late-onset mean age at onset 46.86 years and mode 40 years.

Table 2: Prevalence of comorbid major depressive disorder and posttraumatic stress disorder in obsessive-compulsive patients with late, early and regular onset of the disorder.

Total	Early-onset OCD n=222 (%)	Regular OCD n=676 (%)	Late onset OCD n=85 (%)	Total n=983 (%)	Statistics	P value
MDD Episode						
Current	72 (32.4)	229 (33.9)	26 (30.6)	327 (33.3)	Chi sq. (df = 2) = 0.4	0.8
Past	134 (60.3)	378 (55.9)	46 (54.1)	558 (56.7)	Chi sq. (df = 2) = 1.6	0.4
After age 40	8 (3.6)	35 (5.2)	27 (31.7)	70 (7.1)	Chi sq. (df = 4) = 93.5	< 0.001
PTSD						
A1 criteria	88 (39.6)	264 (39)	29 (34.1)	381 (38.7)	Chi sq. (df = 2) = 0.9	0.6
A2 criteria	62 (27.9)	162 (23.9)	19 (22.3)	243 (24.7)	Chi sq. (df = 2) = 1.7	0.4
Current	28 (12.6)	63 (9.3)	8 (9.4)	99 (10)	Chi sq. (df = 2) = 2	0.3
Past	56 (25.2)	117 (17.3)	14 (16.5)	187 (19)	Chi sq. (df = 2) = 7.2	0.22
After age 40	1 (0.4)	5 (0.7)	5 (5.9)	11 (1.1)	Fisher's exact test	< 0.001

MDD = major depressive disorder; PTSD = posttraumatic stress disorder

PTSD A1 criteria = the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others.

PTSD A2 criteria = the person's response involved intense fear, helplessness or horror.

Table 3: Prevalence of specific life events preceding symptoms in obsessive-compulsive patients with late, early and regular onset of the disorder.

Total	Early-onset OCD n=222 (%)	Regular OCD n=676 (%)	Late-onset OCD n=85 (%)	Total n=983 (%)	Statistics	P value
Obsessions						
Birth	23 (10.3)	67 (9.9)	9 (10.6)	99 (10)	Chi sq. (df = 2) = 0.06	0.9
Pregnancy	1 (0.45)	10 (1.5)	6 (7)	17 (1.7)	Fisher's exact test	0.0017
Any personal problem	64 (28.9)	220 (32.5)	21 (24.7)	305 (31)	Chi sq. (df = 2) = 2.7	0.25
Any family problem	95 (42.8)	253 (37.4)	28 (32.9)	376 (38.2)	Chi sq. (df = 2) = 3.1	0.2
Any personal illness	25 (11.3)	57 (8.4)	3 (3.5)	85 (8.6)	Chi sq. (df = 2) = 4.8	0.09
Change residence	39 (17.6)	147 (21.7)	20 (23.5)	206 (21)	Chi sq. (df = 2) = 2	0.3
Change in cohabitant's behaviour	50 (22.6)	132 (19.5)	11 (12.9)	193 (19.6)	Chi sq. (df = 2) = 3.6	0.16
Recent love, intimate relationships and marriage	30 (13.5)	137 (20.2)	11 (12.9)	178 (18.1)	Chi sq. (df = 2) = 6.8	0.03
Compulsions						
Birth	22 (9.9)	68 (10)	7 (8.2)	97 (9.8)	Chi sq. (df = 2) = 0.3	0.8
Pregnancy	1 (0.5)	9 (1.3)	7 (8.2)	17 (1.7)	Fisher's exact test	< 0.001
Any personal problem	70 (31.5)	215 (31.8)	24 (28.2)	309 (31.4)	Chi sq. (df = 2) = 0.4	0.8
Any family problem	93 (41.9)	271 (40)	28 (32.9)	392 (39.9)	Chi sq. (df = 2) = 2.1	0.3
Any personal illness	26 (11.7)	52 (7.7)	3 (3.5)	81 (8.2)	Chi sq. (df = 2) = 6.3	0.04
Change residence	44 (19.8)	157 (23.2)	22 (25.9)	223 (22.7)	Chi sq. (df = 2) = 1.6	0.4
Change in cohabitant's behaviour	51 (23)	136 (20)	11 (12.9)	198 (20.1)	Chi sq. (df = 2) = 3.8	0.1
Recent love, intimate relationships and marriage	32 (14.4)	141 (20.8)	13 (15.3)	186 (18.9)	Chi sq. (df = 2) = 5.3	0.07
Obsessions and / or Compulsions						
Illicit drug use	2 (0.9)	18 (2.6)	2 (2.3)	22 (2.2)	Fisher's exact test	0.3

Monolayer Network

All relevant variables, regardless of their differences between the groups (as reported in the descriptive analyses) were included in a monolayer network with the outcome of interest being late-onset OCD and the reference group being regular OCD, thus generating a full model (table 4). In this model, the relative risk of each variable with the respective confidence interval was provided.

Table 4: Initial/ Full Model

	Late-onset OCD		Early-onset OCD	
	Coeff./ SE	RRR (95% CI)	Coeff. /SE	RRR (95% CI)
(Intercept)	-4.6/ 1.3	-	0.4/ 0.6	-
Female gender	0.4/ 0.3	1.5 (0.8, 2.8)	-0.3/ 0.2	0.7 (0.5, 1)
Family history of OCS	0.03/ 0.3	1.03 (0.6, 1.8)	0.5/ 0.2	1.6 (1.1, 2.3)
Acute OCS	-1.2/ 0.5	0.3 (0.1, 0.9)	-0.7/ 0.2	0.5 (0.3, 0.7)
Chronic OCS	2.3/ 0.5	10.5 (4.2, 26.4)	-4.5/ 0.7	0.01 (0, 0.04)
Current MDD episode	0.03/ 0.3	1.03 (0.5, 1.9)	0.1/ 0.2	1.1 (0.7, 1.7)
MDD episode in the past	-0.4/ 0.4	0.6 (0.3, 1.4)	-0.1/ 0.2	0.9 (0.5, 1.4)
MDD after age 40	2.7/ 0.4	15.5 (7, 34)	-0.09/ 0.5	0.9 (0.4, 2.3)
No history of MDD	1.1/ 0.4	3.1 (1.3, 7.7)	0/ 0.2	1 (0.6, 1.6)
Trauma A1 criteria	-0.4/ 0.4	0.7 (0.3, 1.5)	-0.3/ 0.3	0.7 (0.4, 1.3)
Trauma A2 criteria	0.4/ 0.6	1.5 (0.4, 5.6)	-0.8/ 0.5	0.4 (0.2, 1.2)
PTSD	0.5/ 0.8	1.7 (0.3, 7.9)	0.2/ 0.4	1.2 (0.5, 2.7)
PTSD in the past	-0.1/ 0.1	0.9 (0.1, 6.2)	1.4/ 0.6	4.2 (1.3, 14)
PTSD after age 40	3.2/ 1	25.8 (3.8, 174.5)	-1.4/ 1.2	0.2 (0.02, 2.7)
No history of PTSD	0.7/ 0.95	2 (0.3, 13.3)	-0.7/ 0.5	0.5 (0.2, 1.2)
Birth				
Obsessions	0.7/ 0.8	2 (0.4, 10.2)	-0.4/ 0.6	0.6 (0.2, 2.1)
Compulsions	-1.6/ 0.9	0.2 (0.03, 1.2)	0.6/ 0.6	1.8 (0.5, 5.7)
Pregnancy				
Obsessions	-1.3/ 2	0.3 (0.01, 13.4)	-0.4/ 3.1	0.7 (0, 290.4)

Compulsions	4.5/ 1.9	90.5 (2.1, 3886.7)	-1.2/ 3.1	0.3 (0, 127.7)
Any personal problem				
Obsessions	-0.4/ 0.6	0.7 (0.2, 2.3)	-1/ 0.4	0.3 (0.1, 0.8)
Compulsions	0.5/ 0.6	1.6 (0.5, 5.1)	0.96/ 0.4	2.6 (1.15, 5.9)
Any family problem				
Obsessions	0.5/ 0.7	1.7 (0.4, 6.5)	1.3/ 0.4	3.6 (1.5, 8.6)
Compulsions	-0.6/ 0.7	0.5 (0.1, 2.1)	-0.9/ 0.4	0.4 (0.1, 0.9)
Any personal illness				
Obsessions	-1.8/ 1.2	0.2 (0.01, 2)	-0.04/ 0.7	0.9 (0.2, 4.1)
Compulsions	0.2/ 1.2	1.2 (0.1, 13.9)	0.6/ 0.7	1.8 (0.4, 8)
Change residence				
Obsessions	-0.4/ 0.8	0.6 (0.1, 3)	0.1/ 0.5	1.1 (0.4, 2.7)
Compulsions	0.3/ 0.8	1.3 (0.3, 6.3)	-0.4/ 0.4	0.6 (0.3, 2.3)
Change in cohabitant's behaviour				
Obsessions	-0.7/ 0.9	0.5 (0.1, 2.8)	1.2/ 0.7	3.4 (0.8, 13.5)
Compulsions	0.1/ 0.8	1.1 (0.2, 5.8)	-0.9/ 0.7	0.4 (0.1, 1.6)
Recent love, intimate relationships and marriage				
Obsessions	-0.3/ 0.7	0.7 (0.16, 3.1)	-0.8/ 0.5	0.45 (0.15, 1.3)
Compulsions	0.04/ 0.7	1 (0.2, 4.6)	-0.2/ 0.5	0.8 (0.3, 2.3)
Drug use				
Obsessions and Compulsions	-0.2/ 1	0.8 (0.1, 6.1)	-1.4/ 0.8	0.2 (0.05, 1.2)

Outcome = onset OCD, Referent group = Regular OCD

Residual Deviance: 1127.19

Akaike Information Criterion = 1255.19

From this initial/full model, a final one was achieved, as described before. In this final model (table 5), all variables were in some way significant, either as a risk or as protective factors. In our case, as the interest were specifically related to risk factors for late-onset OCD, only variables associated with a positive coefficient were included in the late-onset risk factor and correlates final algorithm, which was

eventually formed by female gender, chronic subclinical OC symptoms, PTSD after age 40 and a history of recent pregnancy in self or significant others.

Table 5: Final Model

	Late-onset OCD		Early-onset OCD	
	Coeff./ SE	RRR (95% CI)	Coeff. /SE	RRR (95% CI)
(Intercept)	-3.7/ 0.6***	-	0.7/ 0.3*	-
Female	0.5/ 0.3	1.6 (0.9, 2.7)	-0.2/ 0.2	0.8 (0.6, 1.1)
Acute OCS	-1.2/ 0.5*	0.3 (0.1, 0.8)	-0.6/ 0.2***	0.5 (0.4, 0.7)
Cronic OCS	2.4/ 0.5***	11 (4.6, 26.6)	-4.3/ 0.7***	0.01 (0, 0.05)
PTSD after age 40	2.9/ 0.8***	18.1 (3.8, 87.5)	-1.3/ 1.2	0.2 (0.02, 2.8)
No history of PTSD	0.9/ 0.4*	2.4 (1, 5.8)	-0.9/ 0.2***	0.4 (0.2, 0.6)
Obsessions				
Any family problem	-0.3/ 0.3	0.7 (0.4, 1.2)	0.3/ 1.2	1.3 (0.9, 1.9)
Change residence	-0.01/ 0.3	0.99 (0.5, 1.8)	-0.4/ 0.2	0.7 (0.5, 1.1)
Compulsions				
Birth	-0.9/ 0.5	0.4 (0.1, 1)	0.2/ 0.3	1.2 (0.7, 2.2)
Pregnancy	2.6/ 0.6***	13.2 (3.8, 46.3)	-1.4/ 1.1	0.2 (0.03, 2.1)

Outcome = onset OCD, Referent group = Regular OCD

Residual Deviance: 1240.22
Akaike Information Criterion = 1280.22

The general performance of the final model was tested with the purpose of trying to explain the global variability of late-onset OCD. The obtained Maximum Likelihood and the McFadden R2's values indicated that our last model was able to explain a sizable proportion of the variability related to late-onset OCD, i.e. 29.4% or 21.65%, respectively. A graphic description of our final model is provided on figure 2.

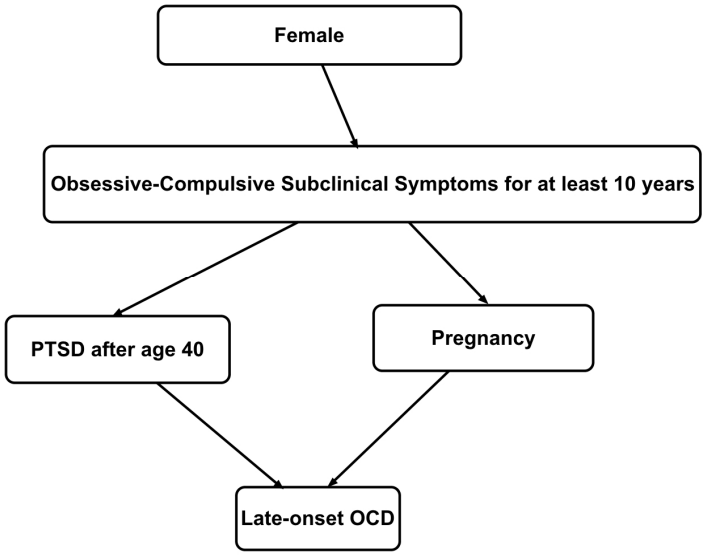

Figure 2 – Late-onset OCD risk factor and correlates final algorithm

Discussion

Our results suggest that late-onset OCD is more likely to occur in females, in individuals with longer periods of subclinical OC symptoms, and in association with a major traumatic event occurring at or after age 40 and a history of recent pregnancy in self or in significant others. The general performance of this model was 29.4%, which is considered quite satisfactory, as compared to studies employing similar strategies in the public health or general medical fields. Also, these results are in agreement with most features of our proposed model of late-onset OCD.

The fact that late-onset OCD was found to be more common among female patients dovetails with different studies reporting that women first exhibit OC symptom at later ages than men. Accordingly, there is plenty of data suggesting that female patients exhibit a differentiated OCD phenotype, as compared to males. For instance, studies reviewed by Mathis et al. indicate that female patients with OCD present more contamination/cleaning symptoms and greater comorbidity with eating and impulse control disorders (Mathis et al., 2011).

We also noted that patients with late-onset OCD exhibited a history of chronic "pre-OCD" subclinical OC symptoms significantly more frequently than regular or early-onset OCD cases. These findings are in broad accordance with the results from an internet based survey of 199 patients with OCD showing that females experienced a significantly longer delay between the development of OC symptoms and full-blown OCD (Coles et al., 2011). We can only offer tentative explanations for these findings. Perhaps cultural perceptions of some OC symptoms, which might be viewed as typical female behaviours (e.g. washing and house ordering), may delay detection of distress and interference associated with OCD. Alternatively, by exhibiting greater ability to accommodate to their OC symptoms and thus avoiding distress and/or interference, female patients may be able to postpone the onset of clinical problems. We speculate that these patients would show full-blown OCD at later ages, particularly after certain distressing events.

Based on this, we have also assessed whether later onset OCD would be associated with a range of precipitating phenomena, including trauma, depression, birth and pregnancy, personal or family problems or illnesses, changes in routine, romantic/intimate relationships or marriage, and drug use (Murphy et al., 2010). As a result, we found that late-onset OCD was particularly related to a major traumatic event occurring after age 40 (as shown by comorbid late-onset PTSD) and to a history of recent pregnancy in self or in significant others.

The fact that late-onset OCD was related to comorbid PTSD is consistent with previous reports suggesting that OCD that develops after traumatic events occurs at later ages (Bhattacharyya and Khanna, 2004). These findings, together with the lack of association between late-onset OCD and a positive family history of OC symptoms, suggest that the former condition may be more likely to be precipitated by psychosocial stressors rather than genetic vulnerability. Indeed, an earlier age at OCD onset has already been linked to a positive family history for OCD (Rosario-Campos et al., 2005).

By showing that a history of recent pregnancy in self or in significant others was more common among late-onset OCD patients, we speculate that the pathophysiology of these cases is more likely to involve changes in hormonal levels. Additionally, for

some individuals, the psychological impact of pregnancy and caring for an infant may bring to the forefront OCD symptoms that may have been present but otherwise subclinical or not severe enough to be detected or to interfere with daily functioning (Forray et al., 2010).

Pregnancy- and post-partum associated fluctuations in hormonal levels are associated with specific parental attitudes (Saltzman and Maestripieri, 2011). For instance, in a study performed during the first postpartum weeks, maternal and paternal oxytocyn levels correlated with affectionate and stimulatory parenting behaviours, respectively (Gordon et al., 2010). In theory, these increased affiliative behaviours may create an appropriate environment for the development of OCD symptoms, particularly in the context of enhanced tension/anxiety found in some postpartum parents (Sekiyama et al., 2013). This effect may not be restricted to female OCD patients (Forray et al., 2010), as males with OCD have also shown reactivation of their OCD symptoms during their wives pregnancies (Petribú et al., 2011).

Our study has a number of limitations. It is a cross-sectional study reporting a model that is supposed to describe pathways toward late-onset OCD. Ideally, the performance of this model has to be tested in a study involving collection of longitudinal data. In addition, some might argue that we lost the opportunity to assess the symptom content of our late-onset OCD cases. In the study by Grant et al., for instance, patients with late-onset OCD exhibited less frequent contamination, religious, or somatic obsessions (Grant et al., 2007).

However, we must underline that, despite a significant amount of research in early vs. late-onset OCD, no consistent or specific pattern of symptom content has been found in late-onset OCD cases (Taylor, 2011). Therefore, it is difficult to raise any hypothesis with regard to symptom dimensions associated with late-onset OCD. Further, it must be noted that our major objective was to unveil developmental pathways towards late-onset OCD rather than any specific phenotypical analysis of its related symptom content. Nevertheless, it remains to be tested, for instance, if late-onset OCD associated with different symptom contents are related to specific developmental pathways (Grisham et al., 2011).

Finally, despite our efforts to isolate a more clear-cut subgroup of patients with late-onset OCD (by setting their minimum age at onset at 40 years old), we cannot exclude the possibility that this subgroup of patients still contained some regular or even early-onset OCD cases. As we considered the presence of distress and interference a hallmark of OCD onset, it could be argued that some particular clinical feature (e.g. poor insight) or environmental circumstance (e.g. availability of parents or siblings) might have delayed clinically significant difficulties among patients who already displayed a true diagnosis of OCD since earlier ages.

According to this later interpretation, older patients might have omitted earlier onset of OCD symptoms because of lack of awareness of illness or for having family members available to accommodate to their symptoms and decrease distress or interference in the past. Although the three groups did not differ in terms of insight levels, and previous research has suggested that family accommodation is associated with greater, rather than lower, severity of OCD symptoms (Ferrão et al., 2006), we found some support for OCD cohabitants functioning as symptomatic buffers, as late-onset OCD patients lived more frequently alone (see table 1). However, we were unable to unequivocally show that a decrease in social support have increased distress in older OCD patients as we did not have any information on social support in other moments of patient's lives.

In conclusion, our findings suggest that late-onset OCD is more likely to occur in females, in individuals with long periods of subclinical obsessive-compulsive symptoms, and in association with a major traumatic event occurring after age 40 and a history of recent pregnancy in self or in significant others.

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Comorbidity in obsessive-compulsive and related disorders

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INTRODUCTION

In the most recent edition of the DSM diagnostic system (DSM-5), obsessive-compulsive disorder is at the core of a new category termed obsessive-compulsive and related disorders (OCRD), together with body dysmorphic disorder (BDD), hoarding disorder (HD), trichotillomania (TM) (hair pulling disorder), and excoriation (skin picking) disorder (APA, 2013). These disorders relate to one another in terms of a range of diagnostic validators. There is a clear clinical utility of grouping these conditions in the same chapter, as clinicians are encouraged to be aware of overlaps between them and to screen for additional OCRD in individuals who present at least one disorder belonging to this group (APA, 2013). Of note, Tourette syndrome (TS) was left out of this category in DSM-5, being classified as a neurodevelopmental disorder, despite its close relationship with obsessive-compulsive disorder (APA, 2013).

Comorbidity in psychiatry refers to the joint occurrence of (i) two or more mental disorders or (ii) a mental disorder and a medical condition (Klerman, 1990). Comorbidity affects research and clinical practice broadly as a result of its influence on diagnosis, treatment, and outcome (Maser & Cloninger, 1990). The appreciation of comorbidity progressively increased in successive DSM editions because of rules that encouraged, rather than discouraged, multiple diagnoses, particularly after DSM-IV. In contrast, early diagnostic systems (e.g. DSM-III) had diagnostic hierarchies, with the more severe and/or pervasive condition taking diagnostic priority over the less severe and pervasive when both were present (Frances, Widiger, & Fyer, 1990).

There is an important differentiation to be made between comorbid and secondary conditions. The designation "secondary" frequently implies that there is a primary event or entity, i.e. something that antedates or causes the "secondary" phenomenon (Samet, Nunes, & Hasin, 2004). For instance, depression that is caused by hypothyroidism is "secondary" to a specific hormonal dysfunction. The association between depression and hypothyroidism in this specific scenario shouldn't be considered a true comorbidity, and the treatment should be targeted at the primary (i.e. hypothyroidism) rather than at the secondary (depression) condition. In contrast, comorbidity implies the need to treat both conditions independently and simultaneously.

Although some critics believe that the more recent diagnostic strategies resulted in reduced attention to differential diagnosis, the identification of comorbid disorders

also generates information that may be clinically useful and relevant for treatment (Frances et al., 1990). For instance, DSM-III did not allow obsessive-compulsive disorder to be diagnosed in TS subjects as obsessive-compulsive disorder was seen as an intrinsic part of TS. However, the therapeutic approach to obsessive-compulsive disorder is clearly different to the one to TS. Thus, while comorbidity rates increased substantially in most recent DSM versions, it also led to better treatments. In this chapter, we reviewed comorbidity studies performed in patients with DSM-5 OCRD and TS.

Comorbidity in Body Dysmorphic Disorder

Body dysmorphic disorder (BDD), formerly known as dysmorphophobia, is a relatively common psychiatric disorder with lifetime prevalence ranging from 0.7% to 2.4% in community settings (Mufaddel, Osman, Almugaddam, & Jafferany, 2013). Most Individuals suffering from BDD develop at least one concurrent psychiatric condition during their lifetimes. For instance, in a study with 293 BDD patients examined for axis I comorbidity, 21.7% of had a single comorbid condition, 28.6% had 2, and 41.4% had 3 or more comorbidities (Gunstad & Phillips, 2003). In this study, the greater the number of comorbidities, the greater the functional impairment. The most common psychiatric comorbidities observed were major depressive disorder, social anxiety disorder, obsessive-compulsive disorder and substance use disorders.

Most studies that have examined the prevalence of BDD in major depressive disorder patients found a high prevalence, with lifetime estimates ranging from 36% (Veale et al., 1996) to 76% (Gunstad & Phillips, 2003). In the largest study, lifetime major depressive disorder was more than twice as common as any other Axis I disorder (Gunstad & Phillips, 2003). Different studies found that atypical major depressive disorder patients have significantly greater rates of comorbid BDD than that do classical major depressive disorder patients (Phillips, Nierenberg, Brendel, & Fava, 1996) (Nierenberg et al., 2002). In major depressive disorder samples, patients with comorbid BDD had an earlier age of onset of depressive symptoms and a longer duration of the current depressive episode (Phillips et al., 1996) (Nierenberg et al., 2002).

At least one study assessed the clinical features and correlates of major depressive disorder in BDD individuals (Phillips, Didie, & Menard, 2007). In this study, subjects

with both conditions had more severe BDD, greater frequency of major depressive disorder in their families, greater rates of comorbid anxiety and personality disorders and increased associated morbidity (i.e. greater social anxiety, increased suicidality, poorer functioning and worse quality of life) than BDD individuals without major depressive disorder. A significant proportion of major depressive disorder subjects (38.2%) had a history of attempted suicide (Phillips, Didie, et al., 2007). Both lifetime BDD severity and lifetime major depressive disorder independently predicted lifetime suicidal ideation (Phillips, Didie, et al., 2007).

In a trial examining time-varying associations between BDD and major depressive disorder, social anxiety disorder and obsessive-compulsive disorder during 1 to 3 years of follow-up, a close and specific relationship between BDD and major depressive disorder was found, as changes in the status of BDD and major depressive disorder were closely linked in time, with improvement in major depression predicting BDD remission, and, improvement in BDD predicting depression remission (Phillips & Stout, 2006). Such relationship was not found between BDD and obsessive-compulsive disorder and social anxiety disorder. Although improvement in obsessive-compulsive disorder predicted BDD remission, BDD improvement did not predict obsessive-compulsive disorder remission, and no significant longitudinal associations were found for BDD and social anxiety disorder (Phillips & Stout, 2006).

Anxiety disorders frequently co-occur with BDD. Over 60% of BDD patients were reported to have a lifetime history of at least one anxiety disorder (Phillips, Siniscalchi, & McElroy, 2004). According to different studies, social anxiety disorder was the most prevalent anxiety disorder in BDD, with the lifetime prevalence varying from 12% (Wilhelm, Otto, Zucker, & Pollack, 1997) to up to 40.3% (Phillips, Menard, Fay, & Weisberg, 2005). The same studies suggested that obsessive-compulsive disorder, then considered an anxiety disorder, was the second most prevalent anxiety disorder in BDD, with lifetime prevalence ranging from 7.7% (Wilhelm et al., 1997) to 38.8% (Phillips et al., 2005). These conditions were followed by panic disorder, which prevalence varied from 5,6% (van der Meer et al., 2012) to 23,1% (Phillips et al., 2005), and generalized anxiety disorder, with prevalence ranging from 2,2% (Phillips et al., 2005) to 7.7% (Wilhelm et al., 1997).

According to a study conducted by Gunstad and Phillips (Gunstad & Phillips, 2003), social anxiety disorder onset often precedes BDD, while panic disorder tends to come

after. In this study, "primary" social anxiety disorder was distinguished from the marked social anxiety symptoms typically caused by BDD, which is expected to begin at the time of, or after, BDD onset. Clinically, however, it can be sometimes difficult to differentiate clinically primary social anxiety from social anxiety symptoms secondary to BDD. Also, the order of onset may be difficult to determine when obsessive-compulsive disorder is comorbid with BDD as patients may show overlapping symptoms (e.g. checking).

Studies that have compared comorbid BDD plus obsessive-compulsive disorder to "pure" BDD or obsessive-compulsive disorder groups found similarities and differences between these groups, and it's unclear whether the comorbid group has greater morbidity. One study suggested that greater severity of depression and suicidality severity in the comorbid group was ascribable to greater BDD severity (Phillips, Pinto, et al., 2007). On the other hand, in a logistic regression analysis performed in a treatment-seeking sample of 901 Brazilian obsessive-compulsive disorder patients, younger age, earlier age at obsessive-compulsive disorder onset, increased severity of depressive and miscellaneous obsessive-compulsive disorder dimension (a specific subgroup of D-YBOCS symptoms), and comorbid social anxiety disorder, dysthymia, anorexia nervosa, bulimia nervosa, and excoriation (skin picking) disorder were all independently associated with obsessive-compulsive disorder comorbidity (which affected 12.1% of the sample) (Conceicao Costa et al., 2012).

Nonweight-related appearance concerns are common in individuals with eating disorders (Dingemans, van Rood, de Groot, & van Furth, 2012) (Kollei, Schieber, de Zwaan, Svitak, & Martin, 2013) as are weight related concerns among patients with BDD (Kittler, Menard, & Phillips, 2007). In fact, both groups share appearance checking, reassurance-seeking, camouflaging, comparison-making, and social avoidance as frequent symptoms (Mitchison, Crino, & Hay, 2013) . The lifetime prevalence of eating disorders in treatment-seeking BDD patients varied from 1.9% in a Dutch study (van der Meer et al., 2012) to 20.5% (Phillips et al., 2005), with controversial results concerning the proportion of specific eating disorders (bulimia versus anorexia).

One study (Ruffolo, Phillips, Menard, Fay, & Weisberg, 2006) found that, compared to BDD patients without eating disorders, patients with both conditions were more likely to be female and less likely to be African American and had more comorbidity

and greater body image disturbance and dissatisfaction. They were also more frequently hospitalized for psychiatric problems and had received a greater number of psychotherapy sessions and psychotropic medications.

In one study (Phillips et al., 2005) describing a wide range of clinical features among BDD patients (n=200), a lifetime prevalence of 40.0% of any personality disorder was described. The most prevalent comorbid personality disorders in individuals under treatment were avoidant (26.9%), obsessive-compulsive (16.8%), borderline (11.8%) and paranoid personality disorder (10.9%) In contrast, the lifetime prevalence of substance use disorders ranged from 30% (Gunstad & Phillips, 2003) to 43.9% (Phillips et al., 2005) in untreated subjects and from 25% (Gunstad & Phillips, 2003) to 50% (Phillips et al., 2005) in patients under treatment. The co-occurrence of BDD and psychotic disorders were also investigated in the same studies, ranging from none (Gunstad & Phillips, 2003) to 3.0% (Phillips et al., 2005).

In sum, BDD is frequently comorbid with major depressive disorder, anxiety disorders (especially social anxiety disorder), obsessive-compulsive disorder, eating disorders, substance use disorders and personality disorders. Improvements in major depression symptoms predict BDD remission, and vice-versa. Social anxiety disorder onset often precedes BDD. However, it can be sometimes difficult to differentiate clinically primary social anxiety from social anxiety symptoms secondary to BDD. An OCD diagnosis in BDD patients is predicted by a diversity of factors including young age, early age at obsessive-compulsive disorder onset, depressive and miscellaneous obsessive-compulsive disorder symptoms, social anxiety disorder, dysthymia, anorexia nervosa, bulimia nervosa, and excoriation disorder.

Comorbidity in Hoarding Disorder

Until recently, many studies evaluating comorbidities associated with hoarding were performed in obsessive-compulsive disorder samples, as hoarding has been considered nothing more than a symptom of obsessive-compulsive disorder and obsessive-compulsive personality disorder (Frost, Steketee, & Tolin, 2011). For instance, a study performed in 1001 Brazilian obsessive-compulsive disorder patients found hoarding to be present in 52.7% of the sample and to be associated with comorbid major depressive disorder, posttraumatic stress disorder, attention deficit/hyperactivity disorder, compulsive buying and tic disorders (Torres et al., 2012). However, hoarding has been also frequently found among patients who seek

treatment for other anxiety disorders, particularly generalized anxiety disorder and social anxiety disorder (Tolin, Meunier, Frost, & Steketee, 2011).

An epidemiological study found that up to 31% of HD patients did not have any comorbidity (Mataix-Cols, Billotti, Fernandez de la Cruz, & Nordsletten, 2013). In a study conducted by Frost and colleagues (Frost et al., 2011), major depressive disorder was the most common comorbid diagnosis, present in 50.7% of the sample, and more frequent than in obsessive-compulsive disorder patients (33.3%). Similarly, Hall and colleagues (Hall, Tolin, Frost, & Steketee, 2013) found depression to be present in 58% of self-identified HD patients. Patients with HD and comorbid depression reacted to discarding items with a feeling of loss or grief which could complicate the implementation of therapeutic strategies in these particular group of patients (Hall et al., 2013).

People may hoard possessions in an attempt to avoid or cope with anxiety and hoarded items might work as a safety behavior in a world perceived as threatening (Frost et al., 2011). In addition, Frost and colleagues (Frost et al., 2011) found generalized anxiety disorder and social anxiety disorder to be the most prevalent comorbid anxiety disorders in HD, with a prevalence of 24.4% and 23.5%, respectively. However, they were not more frequently reported in HD patients than in an obsessive-compulsive disorder control group. In this study, men with HD were more likely to be diagnosed with social anxiety disorder than were men with obsessive-compulsive disorder. As reported above, Tolin et al. (Tolin et al., 2011) found that 29% of generalized anxiety disorder patients and 15% of social anxiety disorder patients had hoarding, which was positively correlated with trait anxiety and depressive symptoms.

Patients with HD were significantly more likely to have experienced a traumatic event than obsessive-compulsive disorder participants, as well as more likely to have experienced a trauma during childhood (Frost et al., 2011). Previous studies have suggested that traumatic experiences occurred prior to the onset of compulsive hoarding (Frost, Krause, & Steketee, 1996). However, comorbidity studies described rates of posttraumatic stress disorder among HD patients ranging from 0 to 23%. These rates were quite similar or even lower than the ones described in other anxiety disorders (Hartl, Duffany, Allen, Steketee, & Frost, 2005) (Frost et al., 2011). In addition, Landau et al. (Landau et al., 2011) found no link between levels of material deprivation and hoarding.

Frost et al. (Frost et al., 2011) reported that 78.3% of HD patients met criteria for at least one acquisition-related impulse control problem, including compulsive buying, kleptomania and excessive acquisition, 40.1% met criteria for two different impulse control disorders, and 6.1% presented all the three investigated conditions. In the same sample, 60.8% of patients had compulsive buying, 59.9% had excessive acquisition of free things and 9.9% had kleptomania. Of note, when compared to an obsessive-compulsive disorder control group, HD participants were more likely to be diagnosed with the above mentioned acquisition-related impulse control problems. In fact, it has been speculated that, rather than comorbidities, these behaviors should be considered part of the hoarding phenotype itself (Frost et al., 2011).

Hoarding symptoms are commonly described in autism spectrum disorders (Pertusa et al., 2010). However, according to a study by Pertusa and colleagues (Pertusa et al., 2012), subjects with HD do not display more autistic traits or poorer theory of mind abilities than individuals with obsessive-compulsive disorder, or any anxiety disorder. Instead, the presence of autistic traits in these individuals was related to the presence of comorbid obsessive-compulsive disorder (Pertusa et al., 2012). In a recent study Ivanov and colleagues (Ivanov et al., 2013) described a rate of 2.9% autism spectrum disorders among hoarders, which was comparable to non-hoarding group.

In the above mentioned study by Frost (Frost et al., 2011), 28% of patients with HD compared to 3% of obsessive-compulsive disorder patients met criteria for attention deficit hyperactivity disorder (inattentive subtype). Hoarding subjects with the comorbid attention deficit hyperactivity disorder had more problems to discard and sort their possessions (Hall et al., 2013), besides, inattentive attention deficit hyperactivity disorder symptoms, but not hyperactivity, was reported to predict severity of HD (Tolin & Villavicencio, 2011). Consistently, Hartl and colleagues (Hartl et al., 2005) found significantly higher rates of attention deficit hyperactivity disorder in adult hoarders when compared with controls. In one recent study (Ivanov et al., 2013), attention deficit hyperactivity disorder was the most common comorbidity (10%) in a HD adolescent population, although the rate was similar to the non-hoarding group. Finally, hoarding symptoms were more common among individuals with self-reported childhood attention deficit hyperactivity disorder than those without attention deficit hyperactivity disorder, specifically attention deficit hyperactivity disorder-inattentive subtype (Fullana et al., 2013).

Also in the Frost's study (Frost et al., 2011), obsessive-compulsive personality disorder was diagnosed in a greater proportion (29.5%) of HD individuals and than in obsessive-compulsive disorder control individuals (16.7%). However, when hoarding was removed from the obsessive-compulsive personality disorder criteria, the two groups did not differ in terms of obsessive-compulsive personality disorder rates, thus suggesting that greater frequency of the later condition in HD is only found if hoarding is considered an obsessive-compulsive personality disorder symptom. These authors also found rates of 8.8% of avoidant personality disorder and 5.4% of borderline personality disorder among hoarding patients.

In an Indian study (Chakraborty et al., 2012), hoarding obsessive-compulsive disorder patients showed a significantly higher frequency of avoidant, dependent, obsessive-compulsive and depressive personality disorders when compared with non-hoarding obsessive-compulsive disorder patients. Finally, an earlier study by Frost and colleagues (Frost, Steketee, Williams, & Warren, 2000) compared obsessive-compulsive disorder patients with and without hoarding symptoms, patients with other anxiety disorders and community controls. Hoarding obsessive-compulsive disorder subjects had more symptoms of avoidant, dependent, obsessive-compulsive, paranoid, schizoid, schizotypal, borderline and narcissistic personality disorders than controls. Nevertheless, only dependent, schizotypal and narcissistic personality disorder symptoms were more frequent in hoarding obsessive-compulsive disorder subjects than in any other group (Frost et al., 2000).

In sum, acquisition-related impulse control problems including compulsive buying, kleptomania and excessive acquisition of free items are the most prevalent "comorbid" conditions in HD. The prevalence of the latter conditions in HD is so high that some have considered it an intrinsic part of the hoarding phenotype itself. Major depression is also a common comorbidity in HD, with rates that are even higher than the ones reported for obsessive-compulsive disorder. Generalized anxiety disorder and social anxiety disorder are the most prevalent comorbid anxiety disorders. High rates of comorbid post-traumatic stress disorder, attention deficit hyperactivity disorder (inattentive subtype) and personality disorder are also found among HD patients.

Comorbidity in Trichotillomania (hair pulling disorder)

Trichotillomania (TM) (hair pulling disorder) is characterized by repetitive hair pulling leading to hair loss and resulting in distress or in functional impairment. After being classified as an impulse control disorder not elsewhere classified for decades, TM was only recently included in the OCRD chapter of DSM-5. Medical complications may occur and there may be irreversible damage to hair growth and hair quality. Around 20% of individuals with hair pulling disorder eat their hair or their hair's root (trichophagia) (Grant & Odlaug, 2008). It can result in a trichobezoar (hair ball), which can block the intestinal tract and, if left untreated, can result in requiring life-threatening emergency surgery (Grant & Odlaug, 2008). TM is often accompanied by other psychiatric disorders. The lifetime prevalence of comorbidities in individuals with TM has been found to be as high as 82% (Odlaug & Grant, 2008b).

Between 42% (Odlaug & Grant, 2008b) and 52% (Lochner, Simeon, Niehaus, & Stein, 2002) of TM patients display a lifetime diagnoses of major depressive disorder, which is also associated with lower quality of life (Odlaug, Kim, & Grant, 2010). Anxiety disorders were also reported to affect a significant proportion of TM patients, ranging from 12.5% (Odlaug & Grant, 2008b) to 73% (Lochner et al., 2002). Generalized anxiety disorder (25%) (Lochner et al., 2002) and social anxiety disorder (14%) (Lochner et al., 2002) were particularly common. A large percentage of hair pullers noticed anxiety as both a precipitator and a consequence of pulling (Woods et al., 2006).

Although less frequently than in excoriation (skin picking) disorder samples, obsessive-compulsive disorder has been described in 8.3% (Odlaug & Grant, 2008b) to 12% (Lochner et al., 2002) of TM patients. While only 1.4% of obsessive-compulsive disorder patients had a diagnosis of TM in one study (Grant, Mancebo, Pinto, Eisen, & Rasmussen, 2006), an Australian group found a lifetime diagnosis of TM to occur in 11.5% (Brakoulias et al., 2011) of individuals with obsessive-compulsive disorder. In a study with obsessive-compulsive disorder patients being treated in a residential facility (severe obsessive-compulsive disorder), 18.8% endorsed any hair pulling, 15.6% had moderate to severe hair pulling, and 7.8% had severe hair pulling (which as comparable to that of a specialty TM clinic population) (Stewart, Jenike, & Keuthen, 2005).

In the latter study (Stewart et al., 2005), obsessive-compulsive disorder patients with moderate to severe hair pulling were more likely to be women, endorse multiple tics, and have earlier-onset obsessive-compulsive disorder. They also tended to have more severe posttraumatic stress disorder symptoms than other obsessive-compulsive disorder patients, but treatment response did not differ between groups. Individuals with obsessive-compulsive disorder and symmetry concerns may also pull out their hair as part of the symmetry rituals. However, in such cases a diagnosis of TM is not given (APA, 2013). Obsessive-compulsive personality disorder was reported in 23% of hair pullers (Lochner et al., 2002).

BDD appears to be less related to TM than to excoriation (skin picking) disorder. Grant and colleagues (Grant, Menard, & Phillips, 2006) interviewed 176 patients with BDD and found that only 2.3% had TM. In fact, individuals with BDD may remove body hair that they perceive as ugly, asymmetrical or abnormal to improve their appearance. However, those individuals do not meet criteria for TM (APA, 2013). The prevalence of BDD in hair pullers is unknown but also seems to be low. Likewise, substance use disorders have been described in no more than 7% of individuals with TM (Odlaug & Grant, 2008b). However, in an Internet study with 1697 hair pullers, 17% and 14% of subjects reported the use of tobacco and alcohol, respectively, to relieve negative feelings associated with pulling (Woods et al., 2006).

As described above, excoriation (skin picking) disorder and TM frequently co-occur. Oldlaug et al investigated 77 patients with excoriation (skin picking) disorder and/or TM and found that up to 24 of these individuals (31%) presented both conditions. This group spent significantly more time picking skin and pulling hair. It also had greater functional impairment than "pure" excoriation (skin picking) disorder and TM groups, although not to a statistically significant degree (Odlaug & Grant, 2008b). At least one comorbid body focused repetitive behaviors was described in 74% of TM individuals, most commonly skin picking (53%), nail biting (32%) and lip/cheek biting (26%). The number of these body focused repetitive behaviors was significantly associated with higher scores of "focused" hair-pulling severity, depression, anxiety, stress and functional impairment (Stein et al., 2008). Nail biting was more common in hair pulling disorder individuals with trichophagia (Grant & Odlaug, 2008).

In sum, a large proportion of TM patients display lifetime diagnosis of major depression disorder and anxiety disorders, specially generalized anxiety disorder and

social phobia. Excoriation disorder, obsessive-compulsive disorder, BDD and other body focused repetitive behaviors (e.g. nose picking, nail biting, and cheek biting) are also frequently reported.

Comorbidity in Excoriation (Skin Picking) Disorder

Excoriation (skin picking) disorder is characterized by the repetitive and compulsive picking of skin leading to integument damage. It results in significant distress, low self-esteem, depressive symptoms, negative body image, social avoidance and poor health (Tucker, Woods, Flessner, Franklin, & Franklin, 2011) (Odlaug et al., 2013). Despite being described for more than a century, excoriation disorder was only recently included in an official diagnostic system. It is currently classified as an OCRD in DSM-5. Medical complications, such as localized and septicemia (generalized infection), are frequent in these individuals and one third of them require antibiotic treatment due to their picking behavior (Odlaug & Grant, 2008a). Non-suicidal self-injury was included in DSM-5 as a condition for further study and involves cutting, burning, stabbing, hitting or rubbing body surface. However, how comorbidity patterns differ between both non-suicidal self injury and excoriation disorder is unclear (McKay & Andover, 2012).

Studies in clinical samples have shown that between 43% (Odlaug et al., 2013) and 100% (Wilhelm et al., 1999) of excoriation disorder patients report a history of at least one comorbid psychiatric condition. Thus, it has been speculated that excoriation disorder may be better conceptualized as a symptom rather than as a disorder. However, studies also describe skin picking disorder preceding the onset and leading to an impairment that seems to be independent from the comorbid conditions (Snorrason, Stein, & Woods, 2013).

Lifetime major depressive disorder has been reported in 26% (Wilhelm et al., 1999) to 58% (Calikusu, Yucel, Polat, & Baykal, 2003) of excoriation disorder patients. The lifetime prevalence of anxiety disorders is more variable, ranging from 2.5% (Odlaug & Grant, 2007) to 65.0% (Wilhelm et al., 1999). However, it is important to note that these data were described when obsessive-compulsive disorder was included in the "anxiety disorders group". Many individuals report that anxiety worsens their picking and some of them find some relief from anxiety while picking. Other patients pick skin to regulate an uncomfortable sensation (e.g. an itching) or a cognitive state (e.g. a concern). Still, picking seems to increase anxiety in other individuals (Tucker et al.,

2011). Thus, excoriation disorder seems to be a heterogeneous condition. It is still not completely clear how these specific features impact comorbid conditions profile.

Studies have consistently found different rates of comorbidity between obsessive-compulsive disorder and excoriation disorder. For instance, rates of obsessive-compulsive disorder in individuals with excoriation disorder ranged from 2.5% (Odlaug et al., 2013) to 52% (Wilhelm et al., 1999). Up to 41% of individuals with obsessive-compulsive disorder present any grooming disorder (Bienvenu et al., 2000), and from 8.9% (Grant, Mancebo, et al., 2006) to 24% (Bienvenu et al., 2000) of them present excoriation disorder. These subjects were more likely to have hoarding, symmetry and repeating compulsions and present more severe obsessive-compulsive disorder symptoms (Grant, Mancebo, et al., 2006). Obsessive-compulsive personality disorder was also frequently reported in individuals with excoriation disorder, with prevalence rates ranging from 19% (Lochner et al., 2002) to 48% (Wilhelm et al., 1999).

Substantial co-occurrence of excoriation disorder and BDD has also been reported, with up to 32% of excoriation disorder patients meeting criteria for BDD (Wilhelm et al., 1999). Grant and colleagues (Grant, Menard, et al., 2006) found that 44.9% of a sample of BDD patients had clinical significant skin picking at the body area with which the subject was excessively preoccupied [although an attempt to improve a perceived defect or flaw is not consistent with excoriation disorder; (APA, 2013)]. Nevertheless, like individuals with excoriation disorder, subjects with BDD that picked their skin as a symptom of BDD were also more likely to present other grooming disorder, such as TM (Grant, Menard, et al., 2006).

Excoriation disorder and TM often co-occur and these pathologies are frequently associated with others body focused repetitive behaviors, such as nose picking, nail biting, and cheek biting. The prevalence of TM in excoriation disorder individuals ranges from 5% (Neziroglu, Rabinowitz, Breytman, & Jacofsky, 2008) to 38.3% (Odlaug & Grant, 2008b). In an Internet study comprising 718 skin picking disorder individuals, 83.4% of the sample presented at least one different body focused repetitive behaviors (Snorrason et al., 2012). Although 47.5% of them reported hair pulling, only 29.7% endorsed DSM-IV criteria for TM. Also, 38% of this sample reported nose picking, 51% nail biting and 47% cheek biting. Interestingly, the body areas from which individuals picked predicted other body focused repetitive

behaviors in that area, e.g. individuals who picked at their scalp were more likely to have hair-pulling problems (Snorrason et al., 2012).

In sum, excoriation disorder is frequently associated with major depression, BDD, TM, obsessive-compulsive disorder, obsessive-compulsive personality disorder, other body focused repetitive behaviors (such as nose picking, nail biting, and cheek biting), and anxiety disorders.

Comorbidity in Olfactory Reference Syndrome

Olfactory reference syndrome — the preoccupation with a false belief that one emits a foul or offensive body odor — has been described for over a century (Phillips & Menard, 2011) but only recently was recognized as a distinct disorder in the DSM-5 chapter on OCRD as "other specified obsessive-compulsive and related disorder" (APA, 2013). Most reports evaluating olfactory reference syndrome consist of case reports or small case series. Those reports assessed a limited range of clinical features, and very few studies investigated the prevalence of comorbid disorders in subjects with olfactory reference syndrome (Prazeres et al., 2010) (Phillips & Menard, 2011).

Major depressive disorder was the most common comorbid condition in olfactory reference syndrome (Prazeres et al., 2010) (Phillips & Menard, 2011). In Phillips et al study (Phillips & Menard, 2011), fifty percent (n=7) of subjects with comorbid major depressive disorder developed olfactory reference syndrome at least 1 year before major depressive disorder, 21.4% (n=3) developed major depressive disorder and olfactory reference syndrome within the same year and 28.6% (n=4) developed olfactory reference syndrome at least 1 year after major depressive disorder onset. Social anxiety disorder, substance use disorders, obsessive-compulsive disorder and BDD were also commonly reported (Prazeres et al., 2010) (Phillips & Menard, 2011)

Comorbidity in Tourette Syndrome

Tourette syndrome (TS) is increasingly recognized as a complex disorder that is associated with a wide spectrum of behavioral problems accompanying motor and phonic tics (Cavanna, Servo, Monaco, & Robertson, 2009). In DSM-5, TS is classified as a neurodevelopmental disorder (although it is likely to be cross-referenced to the OCRD group in ICD-11 (Woods & Thomsen, 2014)). Some have divided TS into (i) pure TS, including primarily of motor and phonic tics; (ii) full-blown TS, including also coprophenomena (involuntary expression of socially

unacceptable words or gestures), echophenomena (automatic imitative actions without explicit awareness), and paliphenomena (repeating own words and actions); and (iii) TS-plus, which comprises cases with severe comorbid neuropsychiatric conditions (Cavanna et al., 2009). Comorbid conditions are found in up to 90% of TS subjects, both in clinical and community settings (Cavanna et al., 2009) (Robertson, 2012) (Wright, Rickards, & Cavanna, 2012). Among children with TS, comorbid disorders frequently leads to greater impairment both in home and school activities (Cohen, Leckman, & Bloch, 2013).

Around 30-50% of children with TS display comorbid attention deficit hyperactivity disorder (Khalifa & von Knorring, 2005), with higher rates in clinical samples. Attention deficit hyperactivity disorder symptoms often precede the tics onset (Freeman et al., 2000). The etiological relationship between TS and attention deficit hyperactivity disorder is unclear, but it is well known that comorbidity leads to worse outcomes, including greater academic and social impairment, but not greater tic severity (Lebowitz et al., 2012) (Cohen et al., 2013).

In studies comparing TS individuals with and without attention deficit hyperactivity disorder, those with only TS did not differ from unaffected controls in many aspects, including aggression, delinquency or conduct difficulties. However, patients with TS and attention deficit hyperactivity disorder displayed significantly higher indices of disruptive behaviors than unaffected controls, which were similar to those presented by the attention deficit hyperactivity disorder group (Robertson, 2012).

The diagnosis of attention deficit hyperactivity disorder increases the odds of meeting criteria for disruptive behavior disorder and is also associated with higher levels of psychosocial stress, poorer functioning, and increased risk for externalizing behavioral problems (Lebowitz et al., 2012). Comorbid attention deficit hyperactivity disorder symptoms in children with tics are responsive to similar pharmacological treatment of attention deficit hyperactivity disorder in children without tics. Screening for attention deficit hyperactivity disorder in individuals with TS is imperative given its prevalence and potential complications (Cohen et al., 2013).

Around one-third to one-half of individuals with TS experience recurrent obsessive-compulsive disorder symptoms (Leckman, Walker, Goodman, Pauls, & Cohen, 1994) (Carter, Pauls, Leckman, & Cohen, 1994) (Khalifa & von Knorring, 2005) (Leckman, Peterson, Pauls, & Cohen, 1997). An exploratory study of 158 young patients with chronic TS showed that children with comorbid obsessive-compulsive disorder (53%

of subjects) experienced more severe tics, increased levels of depressive and anxious symptoms, greater psychosocial stress and poorer global functioning (Lebowitz et al., 2012).

It has also been reported that children with both TS and obsessive-compulsive disorder have more internalizing disorders than TS children without obsessive-compulsive disorder (Cohen et al., 2013). Thus, comorbid TS and obsessive-compulsive disorder might represent a more severe subtype of TS, leading to increased symptomatology of both disorders. This relationship was recently recognized by the inclusion of a tic-related diagnosis of obsessive-compulsive disorder in DSM-5 (APA, 2013).

In contrast, compared to obsessive-compulsive disorder subjects without tics, individuals with tic-related obsessive-compulsive disorder where characterized by a male preponderance, earlier age of obsessive-compulsive disorder onset, poorer response to standard SSRI pharmacotherapy, greater response to augmentation with an antipsychotics, and higher prevalence of first-degree family members with tic disorder (Bloch, Landeros-Weisenberger, et al., 2006) (Hounie et al., 2006). In fact, it has been shown that childhood-onset obsessive-compulsive disorder has a higher genetic load and shared vulnerability with chronic tic disorders (do Rosario-Campos et al., 2005).

When TS and obsessive-compulsive disorder co-occur, obsessions of symmetry or exactness, repeating rituals, counting compulsions, and ordering/arranging compulsions tend to be the most common obsessive-compulsive disorder symptoms (Leckman, Grice, et al., 1994) (Leckman et al., 1997). Also, obsessive-compulsive disorder symptoms in children with TS are more likely to persist into adulthood than the tics themselves (Bloch, Landeros-Weisenberger, et al., 2006) (Bloch, Peterson, et al., 2006). Despite differential responses to pharmacotherapy, obsessive-compulsive disorder patients with or without tic disorders seem to be equally responsive to cognitive-behavioral therapy (Cohen et al., 2013).

In a review on the subject, Robertson (Robertson, 2006) reported that, in 16 uncontrolled studies conducted in specialized centers examining mood changes in 5409 TS patients, depressive symptoms, dysthymia, mood swings and/or major depressive disorder or depressive illness were found in 13 to 76% patients. They also reviewed 13 controlled investigations showing young people and adults with TS

(n=741) to be significantly more depressed than age and gender-matched healthy control subjects using standardized measures.

Clinical correlates of the depression in TS patients include the severity and duration of tic symptoms, the presence of echo- or copro-phenomena, premonitory sensations, sleep disturbances, obsessive-compulsive disorder, self-injurious behavior, aggression, childhood conduct disorder, and possibly attention deficit hyperactivity disorder (Cavanna et al., 2009). As expected, depression in individuals with TS leads to poorer quality of life (Cavanna et al., 2013), and may result in hospitalization and even suicide (Robertson, 2006).

Although the literature indicates that depressive symptoms, including major depressive disorder, are common in TS, the exact nature of their relationship remains unclear. The etiology of depression in TS is unlikely to be caused by a single etiological factor (Cavanna et al., 2009). It might result, for instance, from stigma related to a moderate or severe TS, to a history of bullying during childhood, to other co-occurring disorders (e.g. obsessive-compulsive disorder and attention deficit hyperactivity disorder), to medications used to treat TS (e.g. antipsychotics, alpha-2 agonists or calcium antagonists), or even to a treatment-seeking (Berkson's) bias (Cavanna et al., 2009). It is likely that different factors, or a combination of them, may play a role in specific cases.

In a study investigating a large multisite clinically based sample (the Tourette Syndrome International Database Consortium Registry) comprising 7.288 participants, 4.6% (1 of every 22) of TS subjects had a comorbid pervasive developmental (or autism spectrum) disorder diagnosis, thus suggesting that the risk of autism spectrum disorder increases by 13-fold in TS patients. Also, 99.8% of patients with TS and autism spectrum disorder had at least another comorbid condition, compared to 13.2% in the TS group (Burd, Li, Kerbeshian, Klug, & Freeman, 2009). Male gender, absence of family history of tics/TS and an increased number of comorbidities predicted the presence of autism spectrum disorder in this sample (Burd et al., 2009). Similarly, in a study with 105 children and adolescents with autism spectrum disorder, 24 (22 %) presented tic disorders: 12 TS and 12 with chronic motor tics (Canitano & Vivanti, 2007).

Learning disabilities are also commonly described in TS. Analyzing a subsample of the same Tourette Syndrome International Database Consortium Registry comprising 5.450 subjects, Burd and colleagues (Burd, Freeman, Klug, & Kerbeshian, 2005)

found Learning disabilities in 22.7% of TS subjects, who were also firstly seen earlier, more likely to be males and to have a history of perinatal problems and other comorbidities, and less likely to have multiple family members with tics or TS. Episodic behavioral outbursts and anger control problems are also frequent in TS patients. In a study including a mixed sample of Costa Rican and US TS subjects, 20% of participants had explosive outbursts. In the overall sample, attention deficit hyperactivity disorder, greater tic severity, and lower age of tic onset were strongly associated with explosive outbursts (Chen et al., 2013).

A review suggested disturbed sleeping patterns to occur in 12 to 62% of patients with TS, including nightmares, night terrors, somnambulism, trouble falling asleep, restlessness, talking in sleep, early wakening and separation anxiety in the morning (Mol Debes, 2013). There is also an increased number of personality disorders described in TS clinical patients, which are not restricted to obsessive-compulsive personality disorder (Cavanna et al., 2009). TS subjects have been associated with stubbornness, obstinacy, and inclination to debate (Mol Debes, 2013). It has been suggested that increased prevalence of personality disorders in TS sample could result from long-term outcome of childhood attention deficit hyperactivity disorder, referral bias, or from other childhood psychopathology (Cavanna et al., 2009).

In sum, it is clear that the presence of comorbidities in TS leads to greater impairment and that pattern is different from the disorders in the OCRD group. Major depressive disorder, attention deficit hyperactivity disorder, obsessive-compulsive disorder, autism spectrum disorders, learning disabilities, rage outbursts, sleep disorders and personality disorders are frequently present in TS patients.

Conclusion

The majority of patients diagnosed with OCRD present at least one other DSM-5 condition. The comorbidity rates described in different samples tend to vary according to specific diagnosis. Both BDD and olfactory reference syndrome seem to share a similar pattern of comorbidity that includes major depressive disorder, social anxiety disorder, and obsessive-compulsive disorder. Eating disorders and personality disorders are also frequently reported in BDD patients.

The so-called “grooming disorders”, such as TM and excoriation (skin picking) disorder, tend to co-occur with each other and to be associated with major depressive disorder, anxiety disorders, obsessive-compulsive disorder, BDD and other body

focused repetitive behaviors (e.g. nose picking, nail biting, and cheek biting). Finally, patients with HD exhibit increased rates of comorbid major depressive disorder, anxiety disorders, posttraumatic stress disorder, impulse control disorders, attention deficit/hyperactivity disorder, and personality disorders. The presence of one or more comorbidity seems to determine greater morbidity and significantly reduced quality of life.

TS has a close relationship with obsessive-compulsive disorder and has characterized a specific obsessive-compulsive disorder subtype when comorbid to it. It is frequently comorbid with attention deficit hyperactivity disorder, obsessive-compulsive disorder, major depressive disorder, autism spectrum disorders, learning disabilities, rage outbursts, sleep disorders and personality disorders.

The increased rates of comorbidity in different OCRD can be explained by several factors, including not only common neurobiology but also problems inherent to diagnostic classification in psychiatry (Maser & Cloninger, 1990). Firstly, DSM descriptions of specific disorders tend to simplify the complex clinical picture exhibited by patients presenting to treatment. Secondly, we have witnessed an ever-increasing number of possible diagnoses in the last few years. In terms of OCRD, conditions such as HD and excoriation disorder have now been identified and incorporated officially in DSM. Finally, some diagnostic features, such as intrusive cognitions and repetitive behaviors in OCRD, are now officially shared by multiple conditions.

Some words of caution are needed when examining the literature on comorbidity in psychiatry. As Frances pointed out almost 25 years ago: “To say that conditions are comorbid in a given patient means no more than that the defining descriptive features tend to associate with one another” (Frances et al., 1990). A reification of DSM syndromes, sometimes prematurely upgraded to real “disease entities”, may lead to a fragmented view of a unique patient and to an unintegrated approach to treatment. Naïve clinicians may believe, for instance, that OCD and anxiety disorders are fundamentally distinct and comorbid rather than “holding up the possibility that these are the related surface manifestations of underlying unitary syndromes” (Frances et al., 1990). One should not forget to adopt a cohesive view of the patient and to articulate treatments of different conditions in a coherent fashion that considers the individual as a unique and singular human being.

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Can Neuroimaging Provide Reliable Biomarkers For Obsessive-Compulsive Disorder? A Narrative Review

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Abstract

In this integrative review, we discuss findings supporting the use neuroimaging biomarkers in the diagnosis and treatment of obsessive-compulsive disorder (OCD). To do so, we have selected the most recent studies that attempted to identify the underlying pathogenic process associated with OCD and whether they provide useful information to predict clinical features, natural history or treatment responses. Studies using functional magnetic resonance (fMRI), voxel based morphometry (VBM), diffusion tensor imaging (DTI) and proton magnetic resonance spectroscopy (1H MRS) in OCD patients are generally supportive of an expanded version of the earlier cortico-striatal-thalamus-cortical (CSTC) model of OCD. Although it is still unclear whether this information will be incorporated into the daily clinical practice (due to current conceptual approaches to mental illness), statistical techniques, such as pattern recognition methods, appear promising in identifying OCD patients and predicting their outcomes.

Key words

Obsessive-compulsive disorder; biomarkers; functional magnetic resonance; voxel based morphometry; diffusion tensor imaging; proton magnetic resonance spectroscopy.

Introduction

Obsessive-Compulsive Disorder (OCD) core features are intrusive, unwanted, recurrent and persistent thoughts, urges, or images (obsessions) and/ or repetitive behaviours or mental acts that are performed to reduce anxiety/distress or according to rigid rules [1]. This condition affects up to 3.1% of the general population, leading to decreases in virtually all realms of quality of life and resulting in substantial burden to patients' family members and to society as a whole [2]. Fortunately however, we have witnessed major advances in the management of OCD cases during the last few decades, as serotonin reuptake inhibitors (SRIs) and exposure and response prevention (ERP) are now able to help a substantial amount of patients that would be probably remain symptomatic if living in another era. Advances in the way OCD cases are diagnosed have not paralleled improvements in the way they are treated, though.

Until now, OCD is diagnosed purely on clinical grounds, with neuroimaging playing only a minor role. For instance, neuroimaging in OCD has been only routinely recommended to exclude coarse brain disease in patients firstly exhibiting OCD symptoms after age 40 [3]. In fact, unoptimistic clinicians dispute whether neuroimaging could have any critical role in the diagnosis of any mental disorder, including OCD. To them, if the gold standard for a psychiatric diagnosis is the identification of a specific set of signs and symptoms, it is probably unreasonable to expect that neuroimaging could do any better than the clinician him or herself. While some of these arguments seem reasonable, neuroimaging research may well provide valid biomarkers for OCD in the future, i.e. characteristics that are both objectively measured and indicative of pathogenic processes or predictive of pharmacologic responses to a given therapeutic intervention [4].

The cortico-striato-thalamo-cortical (CSTC) model of OCD is grounded in a dysfunctional communication between the lateral orbito frontal-cortex (OFC) and the ventral striatum (VS) [5]. This model has been based mostly on early studies with positron emission tomography (PET) and single photon emission computed tomography (SPECT) showing hypermetabolism of the head of the caudate nucleus and the orbital gyrus [6]. Recently, the CSTC model of OCD has been expanded to

accommodate other brain areas that also appear to be involved in the pathophysiology of OCD, including the hippocampus, the amygdala, and the parietal cortex circuitry [7-11]. In this article, we will discuss recent imaging studies that attempted to better delineate the pathogenic processes associated with OCD (including the CSTC model) and/or to predict treatment response.

Functional Magnetic Resonance Imaging (fMRI)

Latest reviews and meta-analysis on functional imaging of OCD include fMRI, positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies. They generally converge to show hyperactivity within the OFC [6,12], the caudate nucleus [6,12] and the thalamus [12] of OCD patients as compared to healthy controls. These areas become more active during symptom provocation and less active after effective treatment, either with medication or with cognitive behaviour therapy (CBT) [6,12-14]. Studies with cognitive tasks during functional imaging further support the involvement of those areas in the pathophysiology of OCD [8,14].

Some early pre/ post treatment studies focused in predicting response to treatment of OCD patients, including medication, CBT and even neurosurgery. While decreased regional cerebral blood flow (rCBF) in the OFC was associated with better response to SRIs [15-18], increased rCBF in the posterior cingulate gyrus predicted increased response both to cingulotomy and to fluvoxamine [16,19]. Also, greater rCBF in the right caudate nucleus was associated with better response to paroxetine [20] and increased rCBF in the right cerebellum and left superior temporal gyrus predicted response to fluvoxamine [21]. In contrast, CBT studies in OCD patients have found that increased rCBF in the left OFC [15], higher activation in the temporal pole and amygdala during symptom provocation [22] and the degree of connectivity of the right basolateral nuclei group of the amygdala [23] were all associated with a good therapeutic outcome.

More recent resting state fMRI studies have focused on the analysis of the functional connectivity of the brain. They have found increased [24-31], decreased [32-34] and "unbalanced" (both increased and decreased, depending on the specific regions) [35,36] CSTC connectivity in OCD patients. Additional evidence of the dysfunction

in the CSTC circuit as a potential biomarker in OCD is the intensification [24,31,36] or reduction [33] in functional connectivity in association with increase and decrease in global OCD symptom severity, respectively. Another relevant finding is the increased functional connectivity strength in the CSTC in first-degree relatives of OCD patients [27].

A recent fMRI pattern recognition study investigated whether generic fear-inducing, disgust-inducing, and neutral stimuli could be decoded from brain patterns of single fMRIs of individual OCD patients and healthy controls and whether these differences could provide information to correctly guess subjects diagnostic status [37]. The authors obtained 100% ($p < 10^{-6}$) diagnostic accuracy by using two coordinates of right OFC and one of the left caudate nucleus for the discrimination between groups based on volumes calculated for fear-inducing vs. neutral pictures. Lastly, using a qualitative approach, Peterson and coworkers investigated the diagnostic specificity of resting-state connectivity findings reported in several DSM-IV-TR anxiety disorders (including OCD, posttraumatic stress disorder, social anxiety disorder, specific phobia, panic and generalized anxiety disorder). Among these conditions, OCD was the one most reliably associated with abnormalities in the corticostriatal networks, as well as in the default mode network [38].

Voxel-based morphometry (VBM)

The report of functional abnormalities of the CSTC in OCD was paralleled by increased interest in the possibility of structural brain abnormalities in the same regions. Initial studies employed case-control region-of-interest (ROI) methods. Their most consistent finding was reduced volume of OFC, but there were also significant abnormalities in the striatum, thalamus, amygdala, anterior cingulate cortex (ACC) and hippocampus [8]. The ROI method has several limitations, including the manual delineation of brain regions and the need of an a priori hypothesis [8]. In contrast, structural analysis with voxel-based morphometry (VBM) allows the investigation of both grey and white matter volumes in the whole brain in an automated and unbiased way, without the need of pre-specified regions for investigation [8,39]. The majority of VBM studies only report grey matter results [39].

There are a few meta-analysis of VBM studies that compared OCD patients to healthy controls. Radua et al found increased bilateral regional grey matter volumes in the ventral anterior part of the putamen (lenticular nucleus) and in the caudate nucleus and decreased volumes in the dorsal medial frontal/ anterior cingulate gyrus [40]. According to this meta-analysis, studies that enrolled more severe OCD patients were more likely to report increased grey matter in these regions [41]. In another meta-analysis, Rotge et al reported smaller grey matter density in the supramarginal gyrus, the dorsolateral prefrontal cortex, and the OFC, and greater densities in the basal ganglia (putamen) and the anterior prefrontal cortex [42]. Finally, Peng et al found smaller grey matter volume in the frontal eye fields, medial frontal gyrus and ACC, and increased volumes in the lenticular nucleus, caudate nucleus and right parietal lobules [43].

A recent and comprehensive non-meta-analytical review investigated the consistency and replicability of findings from VBM studies in OCD samples. This review also addressed the relationship between clinical variables and OCD anatomy, which was "a potentially crucial factor that has been systematically examined only in a limited number of studies". The authors found defects in the "affective" fronto-striatal loop of OCD patients, including the OFC, ACC, striatum, thalamus and temporolimbic regions (with volume reductions in the cortex and relative expansions of tissue at the deep grey matter structures and limbic levels). There were also alterations of the "executive" circuits, including reductions in the dorsomedial, dorsolateral, ventrolateral and frontopolar prefrontal cortices, and the associative temporo-parieto-occipital areas. White matter findings showed increased volume of internal capsule and reduced frontal and parietal volume [44].

Piras et al. suggested that increased volume in the medial OFC and internal capsule may contribute more prominently to the severity of OCD symptoms, whereas morphometric alterations in prefrontal, parietal and temporo-occipital regions could be regarded as markers of clinical status and disease progression (e.g. being related to age/duration of illness). Similar attempts to study the relationship between brain volumes and age were also performed by the international OCD Brain Imaging Consortium, which performed a multicenter VBM mega-analysis with 412 adult OCD patients and 368 healthy subjects in 2014. In this study, OCD patients had smaller

volumes of frontal grey and white matter bilaterally, including the ACC and the inferior frontal gyrus extending to the anterior insula and greater cerebellar grey matter bilaterally. A group by age analysis was performed and found relative volume preservation in the putamen, insula and OFC and volume loss in the temporal cortex bilaterally in OCD with increasing age [39].

One study discriminated OCD patients from healthy controls using grey and white matter data analysed with support vector machine (SVM) and Gaussian process classifier (GPC) techniques [45]. The accuracies were all above 75%. Regions with higher discriminative power were the fronto-striatal circuit, the temporo-parieto-occipital junction and the cerebellum [45]. These findings are consistent with the results from a transdiagnostic meta-analysis of VBM studies that enrolled patients with DSM-IV-TR anxiety disorders, which found that patients with OCD had increased bilateral gray matter volumes (vs healthy controls and vs individuals with other anxiety disorders) in the lenticular/caudate nuclei [46]. Finally, attempts to categorize OCD patients according to treatment response were performed by Hoexter et al, who found that left and right medial OFC thickness was a strong predictor of treatment response in treatment naive patients with an accuracy of approximately 80%, sensitivity of 77% and specificity of 81% [47].

Diffusion Tensor Imaging (DTI)

Diffusion Tensor Imaging (DTI) is a MRI procedure that can measure water diffusion inside the brain [48]. Diffusivity is an indirect marker of tissue integrity and fiber directions that made the study the microstructure of the white matter *in vivo* possible [49]. The most used parameters to study DTI are Mean Diffusivity (MD) and Fractional Anisotropy (FA). MD measures the average diffusivity in all directions and is linked to tissue density. FA reflects diffusion direction and is related to fiber orientation. Other parameters less often used are the Axial Diffusivity (AD) and the Radial Diffusivity (RD). The former reflects diffusion parallel to the white matter tracts and allows the identification of axonal alterations, while the latter reflects diffusion perpendicular to the white matter tracts and reveals myelination issues. The FA values are based both on AD and RD [49,50].

In a meta-analysis [43], DTI studies revealed that OCD patients had significantly lower FA in the cingulum bundles, inferior fronto-occipital fasciculus (IFOF), superior longitudinal fasciculus (SLF) and increased FA in the left uncinate fasciculus (UF). Regression analysis showed that OCD symptom severity was associated with decreased FA in the right cingulum bundles. While these findings are not inconsistent with the CSTC model of OCD, reductions of FA values within the IFOF and the SLF also indicate the involvement of the parietal lobes [51-54]. A subsequent review [49] reported decreased FA in the corpus callosum (CC), the cingulum, and the left anterior limb of the internal capsule (ALIC), the latter both in unmedicated [55] and medicated OCD patients [56]. Symptom severity was positively correlated with MD in the corpus callosum (genu), the bilateral ALIC and bilateral SLF [57] and with FA in left middle temporal gyrus [58], as well as decreased FA within the uncinate and the cingulum bundle [59].

Recent DTI studies reporting original data from adults with OCD addressed the value of white matter integrity as an endophenotype for OCD [60] and the ability of DTI to correctly identify OCD patients as so [61]. Fan and coworkers compared FA, AD, RD, and MD values within the corpus callosum, the cingulum bundle, the IFOF and the SLF across unmedicated OCD patients, their unaffected siblings and unrelated healthy controls. They found lower FA values in the left cingulum bundle of OCD patients compared to healthy controls, with the unaffected siblings staying midway between OCD patients and healthy controls, thus suggesting that white matter integrity within the CSTC circuit may be an endophenotype for OCD [60]. At least one study investigated the diagnostic utility of DTI findings in OCD. By employing SVM to FA images from 28 OCD patients and 28 healthy controls, Li and colleagues found that a distributed network including bilateral prefrontal and temporal regions, inferior fronto-occipital fasciculus, superior fronto-parietal fasciculus, splenium of corpus callosum and left middle cingulum bundle was able to correctly identify OCD patients with a sensitivity of 86% and a specificity of 82%, leading to an accuracy of 84% [61].

Other recent and original studies reported the clinical impact of DTI abnormalities in OCD patients, more specifically the relationships between white matter integrity and both cognition [62] and treatment responses [63,64]. In one study comparing 20 OCD

patients to 20 paired healthy controls, white matter integrity was decreased in the OCD patients' orbitofronto-striatal loop, lateral frontal and posterior associative cortices, left SLF, and the body of corpus callosum. In this study, semantic fluency (an ability that was found to predict OCD diagnosis with an accuracy of 90%) correlated with increased MD in left temporal and bilateral parietal regions, and decreased FA in the right posterior corona radiata and the left corticospinal tract [62]. Interestingly, as the white matter integrity in these latter regions did not differ between OCD and healthy controls, semantic fluency impairment was not considered a consequence of primary pathogenic processes.

Fan et al. compared the FA, AD, RD, and MD maps from 15 OCD patients before and after 12 weeks of treatment with different SRIs, including fluvoxamine (6 patients), fluoxetine (4 patients), sertraline (3 patients), and paroxetine (2 patients). Drug treatment resulted in a reduction in RD of the left striatum and right midbrain, and in MD of the right midbrain [63]. Further, the observation that some white matter abnormalities seen in OCD patients may not be rectifiable by adequate treatment was confirmed in a cross sectional study reporting significant decreases in the FA values of the nucleus accumbens among 11 OCD patients who failed to show response to drugs as compared to 11 OCD patients who were not deemed to be resistant to drugs [64]. While the definition of treatment resistance in this latter study was not completely clear, its findings suggest that impairments in reward processing may contribute to lack of appropriate response to treatment in OCD patients [64].

Although it would be interesting to clarify whether white matter integrity findings would be able to differentiate early- from late-onset OCD cases (with potential implications for treatment and outcome), we were unable to identify studies addressing this topic. In fact, recent studies found pediatric or adolescent OCD patients to exhibit abnormalities of white matter integrity that were heterogeneous as those exhibited in the adult literature [65], including defects in the SLF [66,67], the corticospinal tracts [66,68], the splenium [66-69], body [67] and genu [66,67,69] of corpus callosum, the right [67] and left cingulum [66-68], the right [66,67] and left uncinate fasciculus [67] the ALIC bilaterally [67], and the left posterior limb of the internal capsule [67], among others.

In the study by Fitzgerald et al. [35], patients with OCD showed more pronounced

age-related increases in FA than healthy controls in the anterior corpus callosum, anterior cingulum bundle, and the ALIC. Greater FA in anterior cingulum bundle also correlated with more severe symptoms after controlling for age. This interesting finding was interpreted as a reflection of delayed and/or protracted white matter development in pediatric OCD. It was also consistent with other studies showing OCD symptom severity to correlate positively with increased FA in many other white matter tracts, including the ALIC [66] and the splenium of the corpus callosum in pediatric samples [68] and the left middle temporal gyrus in an adult sample [58]. Interestingly, one study found an association between greater FA in the dorsal cingulum bundle and better performance on measures of response inhibition and cognitive control in the absence of differences between OCD and healthy individuals, thus suggesting that some white matter abnormalities be compensatory, allowing OCD patients to perform well in the face of competing and conflicting information [68].

The issue of white matter integrity in pediatric OCD is far from settled though. For instance, in the study by Rosso et al. [70], FA, AD, RD, and MD maps were obtained from 17 children and adolescents with OCD and 19 matched healthy controls. The authors reported significantly lower FA in several white matter clusters of OCD patients, with over 84% of significant voxels localized in a single cluster that encompassed a large expanse of bilateral frontal cortex and extended into the corpus callosum. In contrast to the literature reviewed above, there were no regions of significantly higher FA in OCD children and adolescents compared with controls. Patients also had significantly higher RD in areas that overlapped with the largest cluster of FA reduction. Earlier age at onset of OCD correlated significantly with higher RD in the right corpus callosum and lower FA in the right thalamus, the latter area already implicated in the pathophysiology of early onset OCD. Finally, Gassó and colleagues discovered positive correlations between MD in cerebellar lobes and six genetic polymorphisms related to glutamatergic and dopaminergic pathways in OCD children and adolescents [71].

Proton magnetic resonance spectroscopy (^{1}H MRS)

Proton magnetic resonance spectroscopy (^{1}H MRS) is a non-invasive technique that allows the quantification of certain neurochemical concentrations in many brain

regions, *in vivo*. These neurochemicals includes N-acetyl aspartate (NAA), measured as the total of NAA + N-acetyl aspartyl glutamate (tNAA), creatine (Cre), choline (Cho), myo-Inositol (mI) and Glx, that is composed by Glutamate (Glu) and Glutamine (Gln). So, MRS can be used to characterize metabolic abnormalities in many conditions, such Alzheimer's and Huntington's disease. Since it is a completely non-invasive method, it has the advantage that the same subject can be analyzed multiple times, allowing longitudinal studies and pre and post treatment [72]. Therefore, MRS is widely used to investigate neurological and psychiatric disorders, enabling neurobiological models of disease pathology and providing potential biomarkers [73].

Glutamatergic neurotransmission and homeostasis may be altered in OCD, mainly in the CSTC circuit. There is evidence of these changes coming from animal models, genetic, pharmacological and biochemical studies [74]. There is also interest in the role of glutamate across many conditions characterized by repetitive behaviors other than compulsions, such as stereotypies and impulsivity. Naaijen et al. performed a review including 59 studies investigating fronto - striatal glutamatergic profile with ^{1}H MRS in autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD) and OCD [75]. Despite the disparity of the reviewed studies, the authors were able to report interesting findings, like increased Glx in the striatum across ADHD, OCD and ASD groups and increased Glx in the ACC of paediatric and adolescent ADHD and ASD groups. They also reported decreased Glx in the ACC of adults with ASD and ADHD. Thus, glutamatergic abnormalities occur not only in OCD but also in other disorders characterized by an inability to inhibit behaviors.

In a critical review of the literature on OCD patients' MRS profile, Brennan et al analyzed 28 studies comparing neurochemical levels in OCD patients versus healthy controls, and the changes in patients after treatment with SSRIs or CBT [76]. Although many heterogeneous findings were revealed, the authors were able to find a somewhat consistent MRS profile among OCD patients, including reduced tNAA in the ACC and caudate, reduced Glx in the ACC, increased Glx in caudate and increased tCho in the thalamus, parietal white matter, and hippocampus. Rather than suggesting reversible neuronal loss, reduced tNAA levels in OCD might be potentially reversible, as suggested the normalization of tNAA levels after treatment

with citalopram or CBT. The evidence supporting an effect of CBT over NAA levels were further supported by more recent studies. Atmaca et al. compared the neurochemistry of hippocampus in OCD patients before and after treatment with CBT. The results revealed that NAA levels, which were reduced in patients compared to controls at baseline, increased after treatment [77]. Similar results were also reported by O'Neill et al. who observed lower levels of NAA in pACC OCD patients which increased after CBT [78].

A recent study investigating the ACC, the caudate and the putamen, areas involved in the CSTC circuit, endorsed the previous findings of Brennan's group review by showing lower NAA/Cr in the ACC of unmedicated OCD patients compared with controls. In this latter study, the NAA/Cr ratios in this region were negatively correlated with the total score on the Y-BOCS [79]. However, newer studies did not replicate previous ones or at least minimized the role of glutamate in the pathophysiology of OCD. For instance, using a MRS technique capable of measuring minimally contaminated glutamate levels in three striatal sub regions, Simpson et al. did not show differences between patients and controls [80]. In a recent study, the rostral subdivision of the ACC has been examined by means of MRS and fMRI performed during an emotional counting Stroop task. While the values of Gln/Glu, Glu and Gln did not differ between patients and controls, there was also no association between the deactivation of the rACC during the Stroop task and metabolic levels measured by MRS, thus suggesting that a dysfunctional rACC in OCD is not related to impaired glutamatergic neurotransmission [81].

In order to identify endophenotypic biomarkers for OCD, one study compared the neurochemistry in caudate nucleus, ACC and medial thalamus among OCD patients, non-ill first-degree family members (also termed vulnerability group) and healthy controls [82]. The absolute levels of total tNAA were lower and levels of tCholine, Glx, and myo-inositol were higher in the caudate nucleus and in the ACC of OCD patients as compared to family controls. In contrast, the latter group displayed a similar yet attenuated OCD profile, with lower levels of tNAA and higher levels of tCholine, Glx, and myo-inositol in the same regions as compared to normal controls. A recent study has also highlighted the role of glutamate in early stages of OCD. For instance, Ortiz found no differences in the concentration of Glx in the ACC between

OCD children and adolescents and healthy controls, but the concentrations of Glx were significantly lower in OCD patients with a long duration of the condition (more than 24 months) as compared to patients with a shorter duration [83].

Conclusion

The studies included in this review confirmed and expanded the key role of the CSTC circuit and its limbic connections in the pathogenesis of OCD [84]. Accordingly, structures pertaining to the CSTC circuits have been identified as regions discriminating OCD cases from healthy controls and other anxiety disorder cases in studies using either quantitative (e.g. "classifiers") or qualitative strategies, respectively. In terms of treatment response, thicknesses of the left and right medial OFC have already differentiated responders from nonresponders, with an overall classification accuracy of around 80% [47]. Perhaps in the future pattern recognition methods (such as SVM) will have the potential to be used in the clinical practice. Maybe the classification accuracies will be optimized by combining single or multimodal imaging methods with clinical and psychometric data, thus improving our capacity to predict the course of psychiatric diseases [85,86].

The quest for an ideal biomarker in psychiatry, i.e. one that is associated with high diagnostic specificity and sensitivity and/or is a good predictor of outcome [85] has been complicated by diagnoses that are defined purely on clinical grounds (e.g. on the presence of obsessions and/or compulsions), intermingle with normal behavior [87], are likely to be neurobiologically heterogeneous (e.g. including early- and late-onset forms [88]), and probably share several neurobiological features with one another (e.g. obsessive-compulsive and related disorders) [1]. Thus, although the progress in neuroimaging contributed to a better understanding of psychiatric disorders, there is also a challenge of disentangling a "gordian knot", i.e. different biological traits cutting across health and disease (s). Initiative such as the Research Domains Criteria (RDoC), which acknowledge many of these barriers, may represent a step further in terms of diagnostic tests in the psychiatric science. How these advances may be employed in a discipline that is essentially clinical still needs to be clarified.

Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Subjective and objective impulsivity in obsessive-compulsive disorder

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RUNNING HEAD: Impulsivity in OCD

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Ilana Frydman: Dr. Frydman has made substantial contributions to the conception and design of the paper and the acquisition, analysis and interpretation of data, drafted the first version of the article, and approved of the version to be published.

Paulo Mattos: Dr. Mattos has made substantial contributions to the design, analysis and interpretation of data, revised the paper critically for important intellectual content and approved the version to be published.

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ABSTRACT

BACKGROUNDS AND AIMS: Although a behavioral addiction model of obsessive-compulsive disorder (OCD) has been proposed, there is still insufficient evidence as to whether (i) OCD patients are really behaviorally impulsive, and (ii) self-report and different neurocognitive measures of impulsivity (risk-taking, reflection, and motor impulsivity) are associated in this particular clinical population. **METHODS:** Third-six OCD patients and 35 age-, gender-, education- and IQ-matched healthy controls (HC) filled the Obsessive-Compulsive Inventory-Revised, the Barratt Impulsivity Scale and the Beck Depression Inventory and were evaluated with three components of the Cambridge Neuropsychological Test Automated Battery to assess different aspects of impulsivity, including reward (the Cambridge Gambling Task), reflection (the Information Sampling Task) and motor impulsivity (Stop Signal Task). **RESULTS:** OCD patients did not differ from HC on most neurocognitive parameters, the only exception being deliberation time in the Cambridge Gambling Task, which was increased among OCD patients, but did not correlate with the severity of obsessive, compulsive, impulsive, or depressive symptoms. **CONCLUSIONS:** Despite showing increased impulsivity on self-report measures (particularly attentional impulsivity), our findings are not consistent with the presence of increased objective (neurocognitive) impulsivity levels in OCD. They provide substantial evidence of a differential impulsivity profile within our OCD sample.

Key words: obsessive-compulsive disorder; impulsivity; compulsivity; neurocognition; behavioral addiction

INTRODUCTION

Traditionally, compulsivity and impulsivity are considered opposite ends of a compulsive (risk aversive)-impulsive (reward seeking) spectrum. However, this approach has been criticized for being too simplistic, as these two constructs seem to be orthogonally related (Grant, Potenza, Weinstein, & Gorelick, 2010; Hollander, 1993; Hollander & Wong, 1995) and can actually coexisting in increased levels in the same single OCD and/or impulsive patient (Fontenelle, Mendlowicz, & Versiani, 2005). Evidence of impulsive traits in OCD (Chamberlain, Fineberg, Blackwell, Robbins, & Sahakian, 2006; Ettelt et al., 2007; Penadés et al., 2007) and of compulsive features in addiction and other impulse control disorders (Grant & Potenza, 2006) have contributed to the hypothesis that impulsivity and compulsivity may share common psychopathological and/ or neurobiological mechanisms (Fineberg et al., 2010; Fontenelle, Oostermeijer, Harrison, Pantelis, & Yucel, 2011).

Although the definition of compulsivity has been disputed, it has generally included a "tendency to perform repetitive acts in a habitual/stereotyped manner to attempt to prevent adverse consequences" (Fineberg et al., 2010). In contrast, impulsivity can be defined "as a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to the impulsive individuals or to others"(Moeller, Barratt, Dougherty, Schmitz, & Swann, 2001). Both constructs can be studied at the level of syndrome (disorder, e.g. OCD), behaviour (symptoms, e.g. an isolated compulsive behaviour) or neurocognition (e.g. poor inhibitory control) (Chamberlain, Leppink, Redden, & Grant, 2016). As clinical phenomena, they both have been addressed in comorbidity studies. However, impulsivity can also be assessed by neuropsychological tasks (here termed objective impulsivity) or self-report (similarly termed subjective impulsivity).

In fact, there are brain functional (Figee et al., 2011), neurosurgical (Denys et al., 2010), and neurocognitive (Gillan et al., 2011) evidence of the involvement of the nucleus accumbens and other reward system structures in OCD subjects thought

to be critically important to impulse control and addictive disorders as well (Engel & Cáceda, 2015). Hence, a behavioural addiction model has been recently proposed for OCD in which impulsivity would become more prominent with the progression and severity of the disorder (Kashyap et al., 2012). According to this model, OCD subjects could display decreased resistance, control and insight in relation to their compulsive (particularly motor) behaviours, thus characterizing what some have termed 'impulsive compulsions' (Kashyap et al.,2012; Fineberg et al., 2010; Fontenelle et al., 2011; Grant et al., 2010).

Impulsivity is a multifactorial construct that can operate at different stages of information processing, such as perceptual analysis, goal representation and response execution (Clark, Robbins, Ersche, & Sahakian, 2006). The literature indicates that the main objective/neurocognitive domains of impulsivity are the ability to supress a no-longer required or inappropriate action (motor impulsivity) [measured by go-no-go tasks such as the Stop Signal Task (SST) (Verbruggen & Logan, 2008)]; the difficulty to postpone reward and choose small awards despite negative long-term outcomes (risk-taking) [measured by decision making or gambling tasks such as the Cambridge Gambling Task (CANTAB® [Cognitive assessment software]) ; and the tendency to gather and evaluate information before making a decision (reflection impulsivity) [measured by the Information Sampling Task (Clark et al., 2006)].

In parallel, there are different instruments to measure "subjective" impulsivity, including the Urgency, Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, the Behavioural Activation System and Behavioural Inhibition System Scale, and the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (Dalley & Roiser, 2012). However, the most often used self-report tool to assess impulsivity is the Barratt Impulsivity Scale (BIS). Most studies suggest BIS to measure three underlying constructs, including (a) motor impulsivity, which assesses non-inhibition of incoherent responses and/or acting without thinking; (b) attentional impulsivity, which is related to making quick decisions and/or the inability to focus attention or to concentrate; and (c) non-planning impulsivity, which measures behaviours oriented to the present,

and/or lack of “futuring” or forethought (Malloy-Diniz, Mattos, Leite, & Abreu, 2010; Stanford et al., 2009). There is preliminary evidence suggesting that these factors may be differentially associated with specific brain patterns (Hirjak et al., 2016).

Although many studies suggest objective (Grassi et al., 2015; Penadés et al., 2007;
Boisseau et al., 2012) and subjective (Benatti, Dell’Osso, Arici, Hollander, & Altamura, 2014; Boisseau et al., 2012; Ettelt et al., 2007; Grassi et al., 2015; Sahmelikoglu Onur et al., 2016) impulsivity to be a key feature of OCD, there is still debate on whether OCD is associated with increased levels of impulsiveness. Indeed, it is likely that only some dimensions of impulsivity are affected in OCD individuals, giving rise to heterogeneous findings. For instance, some studies were unable to find differences in terms of motor and/or risk taking impulsivity between OCD patients and healthy controls (Chamberlain et al., 2016; Krishna et al., 2011; Rao, Reddy, Kumar, Kandavel, & Chandrashekar, 2008). These findings have been confirmed by recent meta-analyses, (Abramovitch, Abramowitz, & Mittelman, 2013; Shin, Lee, Kim, & Kwon, 2014; Snyder, Kaiser, Warren, & Heller, 2015; Abramovitch & Cooperman, 2015).

Similarly, reflection impulsivity has been only sparsely assessed in adult (Chamberlain et al., 2007) and juvenile OCD subjects (Hauser et al., 2017). For instance, although reflection impulsivity levels did not differ between adult OCD patients and controls, juvenile samples have shown an increased decision threshold (the opposite of an impulsive decision). There is still no evidence in the literature that the self-report and different neurocognitive measures of impulsivity (risk-taking, reflection, and motor impulsivity) correlate with each other in this particular clinical population or even in others (Broos et al., 2012; Clark et al., 2006). From what has been exposed above, it seems intuitively appealing to consider impulsivity a key ingredient of compulsive (particularly motor) behaviour. However, the topic remains widely understudied. This is unfortunate, as this sort of information could help illuminating the mechanisms underlying compulsive behaviour.

In this study, our aim was to access all the components of subjective and objective impulsivity in OCD subjects and matched controls and investigate whether they are differentially impaired. Based on the behavioural addiction model of OCD and some existing empirical findings (Grassi et al., 2015), we predicted that both subjective and objective impulsivity levels would characterize adult patients with OCD.

METHODS

Subjects

Thirty-six OCD patients and 35 age-, gender-, education-, and IQ-matched healthy controls (HC) were included in our study. Patients have been selected amongst individuals being treated in the OCD clinic of the Institute of Psychiatry of the Federal University of Rio de Janeiro (IPUB/UFRJ) and a few local private clinics, while healthy controls were mostly people from D'Or Institute for Research and Education (IDOR) and IPUB/UFRJ administrative staff. The Ethics Committee of the Federal University of Rio de Janeiro approved this research protocol. A written informed consent was obtained from all participants after the procedures involved were fully explained.

All research subjects were submitted to an initial general assessment performed by a trained psychiatrist (IF), which included the Structured Interview for Disorders of Axis I (SCID) (First, Spitzer, Gibbon, & Williams, 1997); the Structured Interview for DSM-IV Personality (SIDP) (Pfohl, Blum, & Zimmerman, 1997); the Global Assessment of Functioning Scale (GAF) (Hall, 1995); the Yale-Brown Obsessive-Compulsive Symptom Scale (YBOCS) (Goodman et al., 1989); and the Detection test of involvement with alcohol, tobacco and substances (ASSIST) (Humeniuk et al., 2008). The participants also answered the following self-report measures: the Questionnaire from the Brazilian Association of Population Studies (ABEP) (http://www.abep.org/); the Obsessive-Compulsive Inventory – Revised (OCI-R) (Foa et al., 2002) and the Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961).

The inclusion criteria comprised being aged between 18 and 65 years, having at least high school education, a minimum score of 16 on the YBOCS for OCD patients, and minimum score of 60 on the GAF for controls. The exclusion criteria included having comorbid borderline or antisocial personality disorder, alcohol or any substance abuse and increased suicidality, as judged by the interviewer. Almost all OCD patients were under a serotonin reuptake inhibitor (SRI), with the exception of one patient taking valproic acid and olanzapine for comorbid bipolar disorder and another one being treated with a serotonin norepinephrine reuptake inhibitor. Patients' treatment regimen also included antipsychotics (n=14), benzodiazepines (n=14), topiramate (n=2), tricyclic antidepressant (n=1), mirtazapine (n=1) and memantine (n=1). One control was on a serotonin reuptake inhibitor due to major depression fully remitted for more than a year.

Measures

Subjective Impulsivity

Barrat Impulsivity Scale

The Barrat Impulsivity Scale (BIS-11) is the most often used self-report instrument to access personality/behavioural construct of impulsiveness worldwide. It comprises 30 items scored on a Likert scale (ranging from never=1 point to very frequently=4 points). The BIS-11 measures impulsivity on its attentional (e.g. "I don't "pay attention"), motor (e.g. "I do things without thinking"), and non-planning (e.g. "I am more interested in the present than the future") aspects. In this study, we used the validated Brazilian Portuguese version of the BIS-11 (Malloy-Diniz et al., 2010; Stanford et al., 2009).

Objective Impulsivity

We employed three different tasks from the *Cambridge Neuropsychological Test Automated Battery* (CANTAB) in order to access risk taking, motor and reflection impulsivity.

Cambridge Gambling Task

The Cambridge Gambling Task (CGT) was developed to access decision-making and risk-taking behaviour under uncertainty. In this task, the examinee objective should be to accumulate as many points as possible. A computer screen exhibits a row with a variable number of ten red and blue boxes (10 in total). The participant must guess the box colour (red or blue) containing a yellow token underneath. Of note, the ratio of red to blue boxes varies for each trial. The amount of points to be bet is presented in ascending or descending progression, with the participant is instructed to press the button when the number reaches the desired bet amount. After each trial, the subject receives a feedback if he won or lost. The CGT differs from other gambling tasks by distinguish risk-taking from impulsivity as the participant who wants to make a risky bet must wait patiently for it to appear.

We have compared six key outputs from the CGT between OCD and HC, namely delay aversion (i.e. the difference in the percentage bet in the ascending vs. descending bet conditions), deliberation time [i.e. the mean time taken to decide which colour (red vs. blue) to bet on], overall proportion bet (i.e mean percentage of points gambled), quality of decision making [i.e. the fraction of time that the participant chose the most likely outcome (e.g. betting on red when seven red squares and three blue squares are displayed on the screen)], risk adjustment (i.e. the extent to which the bet amount varies with the likelihood of winning), and risk taking (i.e. the mean proportion of points bet on trials where the most likely outcome was chosen) (Clark & Robbins, 2009).

Stop Signal Task

The SST was employed to assess motor impulsivity. Performance in the SST is modelled as a horse race between a “go process”, triggered by the presentation of the “go” stimulus (e.g. an arrow pointing to the left or right), and a “stop process”, triggered by the presentation of the stop signal (such as an auditory

tone) (Verbruggen & Logan, 2008). When the stop process finishes before the go process, the response is inhibited; when the go processes finishes before the stop process, the response is emitted (Verbruggen & Logan, 2008). The SST is divided in two parts. In the first one, involving 16 practice trials, there is an arrow pointing either to the left or to the right and the subject must press a correspondent button according to the direction of the arrow. In the second part, comprising of five blocks of 64 trials with 16 stop trials per block, the subject must refrain from pressing any button if he or she hears an auditory stimulus after the visual one (CANTAB® [Cognitive assessment software]).

In the SST, the probability of pressing a button depends primarily on three outputs: the stop signal delay (SSD), the go reaction time (go RT) and the stop signal reaction time (SSRT) (Verbruggen & Logan, 2008). The SSD is the interval between the "go" stimulus and the stop signal. The SSD is adapted automatically around the 50% performance level by increasing or decreasing the SSD depending on the successful inhibition of the response. Increasing the SSD increases the probability of responding (i.e. if the stop process starts later, it may also finishes later relative to the go process). Increases in the go RT increase the probability of inhibiting, as the stop process may finish before the go process. Finally, an increase in the SSRT (the interval between the stop signal and an estimated stop) maximizes the propensity to press a button, as the stop process may finish after the go process (Verbruggen & Logan, 2008). We also reported the proportion of successful stops (i.e. the proportion of times the participant correctly stopped a response) and detection errors.

Information Sampling Task

The IST was employed to assess reflection impulsivity. It comprises the exhibition of a 5 X 5 matrix of grey boxes hiding a random distribution of blue or yellow squares; these two colours are also displayed at the bottom of a computer screen (Clark et al., 2006). The participants must touch a grey box, which then revels its hidden colour. Participants should choose the colour that predominates on that specific trial at the bottom of the computer screen (Clark

et al., 2006). To this end, the participant is allowed to touch as many boxes as he or she wants to make his or her decision (Clark et al., 2006). The boxes that were opened by the participants remain visible during the whole duration of the trial to minimize the demands on working memory.

The IST comprises two conditions, one fixed and one decreasing win (FW and DW, respectively). While in the FW the participant is awarded 100 points for a correct decision regardless of the number of boxes opened, the number of available points decreased by 10 with every box opened in the DW condition. Thus, in the DW, there is a conflict between reinforcement and certainty (Clark et al., 2006). In other words, subjects who are able to make their decisions while tolerating higher levels uncertainty are more extensively rewarded, whereas subjects who are only satisfied by a high degree of certainty end up winning only very few points per trial.

The following parameters were recorded for each IST condition: mean number of box opened/trial (i.e. the amount of information participants sampled prior to making a decision, (DeVito et al., 2009)), mean P (i.e. the probability that the participant has chosen a colour that was predominant, based on the boxes opened at the time of response, (Bennett et al., 2017)), total correct (i.e. the number of trials for which the subject correctly chose the colour that was in the overall majority, (Solowij et al., 2012)), sampling errors (i.e. the number of trials where the subject chose a colour that was not in the overall majority but was in the majority at the point of decision, (Solowij et al., 2012)), discrimination errors (i.e. when the participant chose a colour that was not at that point in time in the majority, thus making a decision not logically based on the evidence available to them, (Solowij et al., 2012)), and mean box opening latency (i.e. (the time elapsed between the subject opening a box and then opening the subsequent box, (Solowij et al., 2012)).

Statistical Analysis

All analyses were conducted with the Statistical Package for Social Sciences (SPSS) version 21 for Mac (Chicago, SPSS Inc.). Groups (OCD patients and HC) had their sociodemographic and clinical features compared by means of Student's t or Mann-Whitney tests (according to the normality of distribution) and Chi-square tests. As the IST had two conditions, a series of mixed ANOVAs with condition (fixed vs. decreasing) as within-subjects factor and diagnostic status (OCD vs. HC) as between-subjects factor was performed using each IST outcome measure. Performances on the SST and CGT were also compared with of Student's t or Mann-Whitney tests. The adopted level of significance was 0.05. No corrections for multiple comparisons were employed.

RESULTS

The socio-demographic and clinical features of OCD patients and HC are described in table 1. The sample was age-, gender-, education-, and IQ-matched and all OCD patients were symptomatic, with Y-BOCS medium total score of 26.45. As expected, the OCD group had higher scores in the OCI-R and BDI when compared to HC. Regarding subjective impulsivity, we found that OCD patients had statistically significant higher scores in the BIS Attention and Total and a trend in the Non-Planning substrate.

INSERT TABLE 1 HERE

On table 2, we may see the medium and standard deviation of the IST in both OCD and HC. Although there was a significant effect of condition for all IST outcomes (i.e. mean number of box opened/trial [Wilks' Lambda=0.41, F (1, 67)=96.31; p<0.001), mean P [Wilks' Lambda=0.45, F (1, 67)=81.33; p<0.001), total correct [Wilks' Lambda=0.65, F (1, 67)=35.58; p<0.001), sampling errors [Wilks' Lambda=0.74, F (1, 67)=23.33; p<0.001), discrimination errors [Wilks' Lambda=0.90, F (1, 67)=7.40; p=0.008), and mean box opening latency [Wilks' Lambda=0.70, F (1, 67)=28.62; p<0.001]), we were unable to find an interaction

between these variables and diagnosis (i.e. mean number of box opened/trial [F (1,67)=0.25, p=0.87)], mean P [F (1,67)=0.0004, p=0.98)], total correct [F (1,67)=0.52, p=0.47)], sampling errors [F (1,67)=0.97, p=0.33)], discrimination errors [F (1,67)=0.07, p=0.78)], and mean box opening latency [F (1,67)=0.07, p=0.78)]).

INSERT TABLE 2 HERE

No significant difference in any outcome measure of the SST was reported between the OCD group HC groups. In terms of the CGT, the only significant difference between the groups was a higher deliberation time in the OCD group (table 3). The lack of relationship between test performance and severity of both BDI and most OCI-R scores is depicted in the supplementary material.

INSERT TABLE 3 HERE

DISCUSSION AND CONCLUSIONS

In this study, we have performed a broad assessment of impulsivity levels in OCD patients, both in terms of their subjective (attentional, motor and non-planning) and objective (reward/risk-taking, motor and reflection impulsivity) aspects, which were then compared to those of age-, gender, education, and IQ matched controls. Despite predicting that adult OCD patients would present increased levels of impulsivity (as suggested by the behavioral addiction model of OCD), we found impulsivity in OCD to be restricted to its subjective (particularly attentional impulsivity) component, rather than extending to more objective tests. These findings suggest that, despite perceiving themselves a impulsive, adult OCD patients do not show any “hard” (or behavioral) evidence of such abnormalities.

While the finding of increased BIS scores in the absence of objective impulsivity seems intuitive on the basis of phenomenological accounts of OCD patients [who frequently report not feeling “in control” when they actually are (Luigjes, 2015)],

the fact that increased subjective impulsivity in our OCD sample could be credited mostly to greater attentional impulsivity has already been described in previous quantitative studies of OCD (Benatti et al., 2014; Ettelt et al., 2007; Grassi et al., 2015; Sahmelikoglu Onur et al., 2016) and other anxiety disorders (Summerfeldt, Hood, Antony, Richter, & Swinson, 2004). Actually, when one learns that attentional impulsivity has been related to the inability of "deleting no-longer-relevant information" from working memory (Whitney, Jameson &, Hinson, 2004), it is not difficult to understand why OCD samples display increased attentional impulsiveness.

Our findings regarding objective impulsivity are consistent with the literature. For instance, previous studies with the CGT did not find evidence of an impaired CGT performance in OCD (Chamberlain, 2007; Chamberlain et al., 2007; Dittrich & Johansen, 2013; Chamberlain et al., 2016). In fact, most studies that reported impaired "decision-making" in OCD used the Iowa Gambling Task (Cavedini et al., 2012; H. W. Kim et al., 2015; da Rocha, Alvarenga, Malloy-Diniz, & Corrêa, 2011), which has been criticized for being unable to isolate risk preference from working memory abilities due to its emphasis on learning that the task demands (Clark & Robbins, 2009). Instead, our OCD patients showed increased deliberation time in CGT, i.e. the mean time taken to choose a box color, a parameter that provides a measure of pre-motor processing and movement time after the decision-making information is presented. Prolonged deliberation time has been reported in long-term alcohol abuse and victims of accidents or injuries (CANTAB® [Cognitive assessment software]).

We were unable to find differences in the SST performance between OCD and HC. Although most studies report impaired motor response inhibition in OCD samples (Boisseau et al., 2012; Chamberlain, 2007; Chamberlain et al., 2006; Penadés et al., 2007), a recent meta-analysis showed only small to medium effect sizes in the SST reaction times (Snyder et al., 2015). It is tempting to speculate that differences between studies may depend on the severity of over (motor) vs. covert (mental) ritualistic behaviors. Although we are not aware of specific instruments available to measure these specific symptoms in a reliable manner,

future studies could consider comparing SST performance between OCD subjects with predominant motor vs. mental rituals. Finally, lack of differences in the IST performance of OCD vs. HC extends and confirms the findings of (Chamberlain et al., 2007) showing lack of reflection impulsivity impairment in OCD.

Dissociation between subjective and objective impulsivity in our OCD sample dovetails with studies showing that self-report and laboratory behavioral assessments of impulsivity are not highly related to each other (e.g., (Mitchell, 1999; Reynolds, Ortengren, Richards, & de Wit, 2006). We can only speculate on the reasons for this dissociation within our sample. For instance, in light of previous studies showing increased rates of attention deficit hyperactivity disorder in OCD patients (de Mathis et al., 2013), future projects could investigate whether increased subjective impulsivity in OCD adults is akin to a "cognitive scar" that reflects the presence of an early objective impulsivity that vanishes later due to the progressive maturation of fronto-subcortical circuits. In order to clarify the true relationship between subjective and objective impulsivity in OCD, longitudinal studies are badly needed.

Our study has some limitations. Firstly, it could be argued that lack of "objective" impulsivity in our OCD sample could reflect the fact that almost all patients were under a SRI, a family of drugs that could, at least theoretically, decrease levels of impulsivity. Although we agree that the recruitment of non-medicated individuals could have increased the reliability of our findings, there are a number of reasons to suggest that SRIs haven't played a major role in test performance. For instance, motor (Bari, Eagle, Mar, Robinson, & Robbins, 2009) and reward (Baarendse, Winstanley, & Vanderschuren, 2012) impulsivities do not seem to be unequivocally impacted by serotonergic manipulation. Further, despite some findings suggesting that serotonin may affect reflective impulsivity (Crockett, Clark, Smillie, & Robbins, 2011) one should also be consider that all of our OCD patients were still substantially symptomatic [mean YBOCS = 26.45 (5.85)] despite appropriate SRI treatment.

Secondly, a few relevant phenotypic features, such as age at OCD onset, haven't

been assessed in our sample. Bearing in mind theories (such as the behavioral addiction model of OCD) suggesting that increased impulsivity may be restricted to patients with longer duration of illness (Kashyap et al., 2012), it would have been interesting to clarify whether our sample was characterized mostly by recent onset OCD cases. Although we are unable to disregard this possibility, there are reasons to believe this hasn't been the case. In fact, our sample included mostly adult patients [mean age at assessment = 37.97 (13.58) years]. As OCD has been argued to start in child and adolescent years in up to 80% of cases (Grados, Labuda, Riddle, & Walkup, 1997), it is reasonable to speculate that our patients were mostly chronic individuals with a long history of OCD. In other words, although there is still a lot to clarify in terms of the cognitive phenotypes of OCD patients, our findings provide substantial evidence of a differential impulsivity profile within our sample.

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Table 1: Socio-demographic, clinical features and cognitive impulsivity of obsessive-compulsive disorder vs. healthy control sample

	OCD (SD); n=35	HC (SD); n=35	Statistical tests
Socio-demographic features			
Age	37.97 (13.58)	36.68 (11.61)	t=0.42 df=68; p=0.67
Gender (male)	62.8%	48.6%	χ2=1.44; df=1; p=0.22
GAF	46.43 (7.91)	93.17 (5.68)	t=-28.38; df=68; p<0.001
Education	14.54 (2.10)	15.28 (2.55)	t=-1.32; df=68; p=0.19
IQ	93.64 (19.53)	96.10 (9.77)	t=-0.66; df=67; p=0.51
Severity of symptoms			
OCI-R total	25.91 (12.31)	5.79 (5.33)	Z=-6.40; p<0.001
BDI	16.98 (942)	4.00 (4.09)	Z=-6.43; p<0.001
BIS			
Attention	19.43 (3.76)	15.3 (3.33)	t=4.72; df=65; p<0.001
Motor	18 (3.39)	17 (2.68)	t=1.33; df=65; p=0.18
Non-planning	26.78 (4.71)	24.06 (3.11)	t=2.75; df=63; ; p=0.08
Total	64.47 (9.06)	56.59 (6.69)	t=3.95; df=62; p<0.001
YBOCS			
Obsessions	13 (3.3)	---	
Compulsions	13.45 (3)	---	
Total	26.45 (5.85)	---	

Footnote: OCD= Obsessive-Compulsive Disorder; HC= Healthy Controls; GAF= Global Assessment of Functioning Scale; IQ= Intelligence Quotient; OCI-R= Obsessive-Compulsive Inventory – Revised; BDI= Beck Depression Inventory; BIS= Barrat Impulsivity Scale; Y-BOCS= Yale-Brown Obsessive-Compulsive Symptom Scale.

Table 2: Stop Signal Task and Cambridge Gambling Task performances of obsessive-compulsive disorder patients vs. healthy control subjects

	OCD (n=36)	Healthy controls (n=35)	Statistical tests
Cambridge Gambling Task			
Delay aversion	.28 (.19)	.34 (.24)	t=-1.086; df=66; p =.28
Deliberation time	3450.31 (1891.65)	2393.11 (734.72)	t=3.003; df= 66; p=.004*
Overall proportion bet	.51 (.17)	.47 (.15)	t=.996; df= 66; p=.244
Quality of decision	.85 (.16)	.89 (.13)	t=-1.176; df=66; p=.244
Risk adjustment	.96 (1.18)	1.21 (1.33)	Z=-.89; p=.37 (t=-.812; df=66; p= .42
Risk taking	.55 (.18)	.51 (.16)	t=.85; df=66; p=.395
Stop Signal Task			
Detection errors stop and go	3.12(3.92)	2.28 (2.71)	Z=-.89; p=.37 (t= 1.028; df= 68; p= .307)
Proportion of successful stops	.50 (.12)	.51 (.12)	t=-.27; df=68; p=.79
Median correct reaction time on go trials	547.82 (181.62)	517.24 (147.81)	t=.77; df=68; p=.44
Stop signal delay	342.25 (171.22)	337.79 (148.88)	t=.116; df=68; p=.44
Stop signal reaction time	205.56 (85.85)	179.447 (47.23)	t=1.57; df=689; p=.12

Footnote: OCD= Obsessive-Compulsive Disorder

Table 3: Information Sampling Task performance of obsessive-compulsive disorder patients vs. healthy control subjects

	OCD (n=36)	Healthy controls (n=35)
Information Sampling Task		
W/condition fixed		
Mean number of box opened/trial	13.75 (6.4)	15.67 (5.63)
Mean P	.78 (.13)	.83 (.12)
Total correct	8.37 (1.64)	8.63 (1.14)
Sampling errors	1.03 (1.12)	1.09 (1.13)
Discrimination errors	1.00 (1.44)	.54 (.87)
Mean box opening latency	1264.71 (1003.87)	965.26 (626.27)
W/condition decreasing		
Mean number of box opened/trial	7.77 (3.57)	9.40 (4.63)
Mean P	.67 (.09)	.71 (.10)
Total correct	7.31 (1.73)	7.79 (1.47)
Sampling errors	1.91 (1.42)	1.70 (1.36)
Discrimination errors	1.57 (2.25)	1.00 (1.84)
Mean box opening latency	2092.63 (1588.1)	1887.94 (1539.26)

Footnote: OCD= Obsessive-Compulsive Disorder

	BDI	OCI-R						
		Checking	Hoarding	Neutralization	Obsessing	Ordering	Washing	Total
Information sampling task								
W/ condition fixed								
Mean number of box opened/trial	r=-.267; p=.115	r=-.305; p=.070	r=-.033; p=.847	r=-.020; p=.908	r=-.022; p=.899	r=-.053; p=.760	r=.012; p=.943	r=-.120; p=.487
Mean P (correct)	r=-.242; p=.154	**r=-.334; p=.047**	r=.021; p=.904	r=.017; p=.921	r=-.014; p=.934	r=-.041; p=.813	r=.058; p=.738	r=-.081; p=.637
Total correct	r=-.242; p=.155	r=-.233; p=.172	r=-.009; p=.957	r=.044; p=.798	r=.006; p=.974	r=.011; p=.947	r=.128; p=.458	r=-.006; p=.974
Sampling errors	r=.170; p=.322	r=.128; p=.458	r=.047; p=.787	r=-.071; p=.679	r=-.026; p=.881	r=-.123; p=.476	r=-.216; p=.206	r=-.092; p=.594
Discrimination errors	r=.186; p=.276	r=.298; p=.077	r=-.041; p=.814	r=-.056; p=.746	r=-.017; p=.920	r=.091; p=.597	r=-.009; p=.958	r=.075; p=.662
Mean box opening latency	r=.076; p=.658	r=.080; p=.644	r=.091; p=.599	r=.045; p=.794	r=-.057; p=.741	r=.108; p=.530	r=-.105; p=.542	r=.035; p=.838
W/ condition decreasing								
Mean number of box opened/trial	r=-.022; p=.901	r=-.083; p=.629	r=-.102; p=.554	**r=.448; p=.006**	r=.302; p=.074	r=-.091; p=.597	r=.181; p.291	r=.221; p=.194
Mean P (correct)	r=--.043; p=.804	r=-.103; p=.549	r=-.158; p=.357	**r=.422; p=.010**	r=.208; p=.223	r=-.103; p=.552	r=.074; p=.670	r=.126; p=.465
Total correct	r=.034; p=.844	r=-.254; p=.134	r=-.305; p=.070	r=.310; p=.066	r=.112; p=.514	r=.033; p=.847	r=.190; p=.267	r=.061; p=.726
Sampling errors	r=-.056; p=.746	r=.149; p=.387	r=.218; p=.202	r=-.168; p=.327	r=.018; p=.919	r=-.130; p=.451	r=-.149; p=.385	r=-.041; p=.811
Discrimination errors	r=.181; p=.291	r=.033; p=.850	r=.044; p=.797	r=-.243; p.154	r=-.108; p=.530	r=.098; p=.570	r=.063; p=.716	r=-.040; p=.817
Mean box opening latency	r=.088; p=.611	r=-.123; p=.476	r=-.058; p=.736	r=-.106; p=.537	r=-.204; p=.234	r=-.026; p=.878	r=-.094; p=.584	r=-.183; p=.285
Stop Signal Task								
Detection errors stop and go	r=-.270; p=.112	r-.084; p=.627	r=-.018; p=.919	r=-.103; p=.551	r=-.096; p=.577	r=-.104; p=.548	r=-.157; p=.359	r=-.173; p=.312
Proportion of successful stops	r=.147; p=.391	r=.000; p=.999	r=-.046; p=.791	r=.164; p=.339	r=.185; p=.280	**r=.332; p=.048**	r=-.125; p=.469	r=.140; p=.416
Median Correct RT on go trials	r=.411; p=.013	r=.098; p=.568	r=-.001; p=.996	r=.130; p=.448	r=.076; p=.660	r=.324; p=.054	r=.160; p=.351	r=.237; p=.164
Stop Signal Delay	r=.310; p=0.66	r=.147; p=.392	r=.036; p=.836	r=.118; p=.493	r=.091; p=.596	r=.141; p=.412	r=.145; p=.399	r=.205; p=.229
Stop Signal Reaction Time	r=.256; p=.132	r=-.087; p=.613	r=-.075; p=.665	r=.041; p=.812	r=-.022; p=.898	**r=.412; p=0.12**	r=.050; p=.771	r=.093; p=.590
Cambridge Gambling Task								
Delay aversion	r=-.037; p=.831	r=-.020; p=.906	r=.024; p=.888	r=-.228; p=.180	r=-.018; p=.918	r=.163; p=.342	r=-.073; p=.674	r=-.061; p=.725
Deliberation time	r=.154; p=.368	r=-.197; p=.250	r=.155; p=.365	r=-.071; p=.679	r=.024; p=.891	r=.120; p=.486	r=.105; p=.541	r=.034; p=.844
Overall proportion test	r=-.163; p=.344	r=-.123; p=.474	r=.095; p.581	r=-.114; p=.509	r=.075; p=.664	r=.132; p=.443	**r=-.482; p=.003**	r=-.165; p=.337
Quality of decision	r=-.165; p=.335	r=-.250; p=.141	r=-.134; p=.434	r=-.002; p=.992	r=-.106; p=.539	r=-.083; p=.629	r=-.086; p=.619	r=-.190; p=.268
Risk adjustment	r=-.138; p=.421	r=-.200; p=.243	r=-.263; p=.120	r=.324; p=.054	r=-.036; p=.836	r=-.294; p=.082	r=-.107; p=.535	r=-.145; p=.397
Risk taking	r=-.151; p=.379	r=-.095; p=.580	r=.050; p=.770	r=-.073; p=.671	r=.075; p=.663	r=.083; p=.629	**r=-.486; p=.003**	r=-.169; p=.325

*supplementary material

Decoding Moral Emotions in Obsessive-Compulsive Disorder

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Abstract

Background:

Patients with obsessive-compulsive disorder (OCD) exhibit abnormal neural responses when they experience particular emotions or when they evaluate stimuli with emotional value. Whether these brain responses are sufficiently distinctive to discriminate between OCD patients and healthy controls is unknown. The present study is the first to investigate the discriminative power of multivariate pattern analysis of regional fMRI responses to moral and non-moral emotions.

Method:

To accomplish this goal, we performed a searchlight-based multivariate pattern analysis to unveil brain regions that could discriminate 18 OCD patients from 18 matched healthy controls during provoked guilt, disgust, compassion, and anger. We also investigated the existence of distinctive neural patterns while combining those four emotions (herein termed *multiemotion* analysis).

Results:

We found that different frontostriatal regions discriminated OCD patients from controls based on individual emotional experiences. Most notably, the left nucleus accumbens (NAcc) discriminated OCD patients from controls during both disgust and the multiemotion analysis. Among other regions, the angular gyrus responses to anger and the lingual and the middle temporal gyri in the multi-emotion analysis were highly discriminant between samples. Additional BOLD analyses supported the directionality of these findings.

Conclusions:

In line with previous studies, activity in regions beyond the frontostriatal circuitry also differentiates OCD from healthy volunteers. The finding that the response of the left NAcc to different basic and moral emotions is highly discriminative for a diagnosis of OCD confirms current pathophysiological models and points to new venues of research.

Key words: moral emotion, sentiment, fMRI, obsessive-compulsive disorder

1- Introduction

Obsessive-Compulsive Disorder (OCD) is characterized by intrusive and repetitive thoughts, urges or images that cause anxiety and distress (obsessions) which are momentarily relieved by mental or motor acts (compulsions)(APA, 2013). OCD is a chronic, disabling, and relatively common disorder, affecting up to 3% of the general population(Fontenelle and Hasler, 2008). Although there is a consensus in the literature that OCD patients exhibit abnormalities in the cortico-striato-thalamo-cortical (CSTC) circuitry(Saxena et al., 1998; Whiteside et al., 2004), emerging evidence supports the involvement of other regions, such as the hippocampus, the amygdala and the parietal cortex (Menzies et al., 2008; Milad and Rauch, 2012; Nakao et al., 2014). Thus, not surprisingly, OCD is a pleomorphic disorder, involving heterogeneous cognitive (i.e. obsessions), affective (e.g. emotions), and behavioral (i.e. compulsions) symptoms, each of them with a wide range of possible contents or "themes".

Broadly speaking, OCD defining symptoms (obsessions and compulsions) can be classified into four main dimensions, i.e. contamination with washing, thoughts of harm with checking, symmetry and organization, and taboo/blasphemous thoughts with mental rituals (Abramowitz et al., 2010). However, the fact that OCD involves more emotions than just anxiety or distress was not formally been recognized before the publication of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), which removed OCD from the anxiety disorders chapter and highlighted that OCD patients often exhibit abnormal feelings of disgust and incompleteness.

In addition to basic emotional abnormalities as a core part of OCD psychopathology (Lawrence et al., 2007; Moscovitch et al., 2008; Starcke et al., 2009; Whiteside and Abramowitz, 2005), there are also broader affective problems among OCD patients,

including the appraisal (Calamari et al., 2008; Calkins et al., 2013), expression (Bersani et al., 2012; Pasquini et al., 2010) and recognition (Aigner et al., 2007; Bersani et al., 2012; Corcoran et al., 2008; Montagne et al., 2008) of different kinds of emotions as compared to healthy subjects. Furthermore, there is growing evidence that OCD patients exhibit heightened emotional (Becker et al., 2014; Schienle et al., 2005) and moral sensitivities (Braun et al., 2008; Harrison et al., 2012; Salkovskis et al., 1999). Thus, attempts to clarify the role of emotional processing deficits in the pathophysiology of the OCD seem warranted. Clearly, paradigms that involve the induction of different types of emotions represent an important component of such studies.

fMRI studies investigating the neuroanatomical basis of OCD have employed cognitive (e.g. reversal learning paradigm) (Remijnse et al., 2009), symptom provocation (e.g. the Maudsley obsessive-compulsive stimuli set) (Mataix-Cols et al., 2009), and emotional (e.g. face recognition) tasks. Although these studies have helped to establish a pathophysiological model of OCD, several gaps remain. For instance, cognitive tasks do not usually consider OCD symptom *content*, which can be extremely variable across individuals. In contrast, provocation of symptoms in OCD can be quite challenging, since a stimulus (e.g. a doorknob) that provokes symptoms in one individual (e.g. a checker) may not provoke it in another (e.g., an arranger), prompting studies to include patients from a restricted OCD subgroup (e.g. washers) tested against specific stimulus (e.g. contamination) (Gilbert et al., 2009; Olatunji et al., 2014; van den Heuvel et al., 2004).

Differently from basic emotions, which are shared by most mammals, moral emotions are unique human features that reflect the interests or welfare of the society as a whole or of persons other than the judge or agent (Haidt, 2003). Moral motions foster prosocial behaviors associated with cooperation, helping, reparative actions as well as social

reciprocity (including happiness, guilt, compassion and gratitude); yet, moral emotions also favor avoidance and aggression, such as when witnesses a violation of norms and rights, which induces specific emotional states, typically moral disgust (contempt) and moral anger (indignation) (Haidt, 2003; ZAHN et al., 2012). Moral emotions are in general more complex than basic emotions, and are thought to emerge as neural representations that rely on the activation of a distributed brain network coding for the perception of social cues (temporoparietal junction), social conceptual knowledge (anterior temporal cortex), abstract event sequence knowledge (prefrontal cortex), and basic emotional states (rostromedial basal forebrain) (Moll et al., 2008).

Investigation of the neural basis of moral emotions is an emerging field that is clarifying the symptomatic expression and pathophysiology basis of many psychiatric disorders. It may be especially relevant in OCD (Fontenelle et al., 2015) and related disorders. For instance, research has found disgust to be particularly relevant in contamination fears/washing compulsions (Olatunji et al., 2017), while guilt/compassion seems to be implicated in taboo thoughts/checking compulsions (Melli et al., 2017); and anger associated with symmetry/ordering symptoms (Whiteside and Abramowitz, 2005). Thus, deficits in the way different frontotemporal and subcortical regions process moral emotions can contribute to the pleomorphic symptomatic expression exhibited by individual patients. In addition, there may also be brain regions whose dysfunction may not be emotion-specific, but rather implicated in a generalized deficit in the processing moral emotions. Thus, in this study, we investigated the brain regions engaged by the experience of guilt, compassion, anger and disgust and to what extent they differentiated patients with OCD from controls.

2 - Methods and Materials

2.1 - Subjects

A sample of 38 DSM-IV OCD and 34 healthy controls were initially assessed for participation in our study. Patients have been selected amongst individuals being treated in the OCD clinic of the Institute of Psychiatry of the Federal University of Rio de Janeiro (IPUB/UFRJ), while healthy controls were mostly people from the D'Or Institute for Research and Education (IDOR) and IPUB/UFRJ administrative staff. After careful matching for socio-demographic and behavioral performance, 18 OCD and 18 healthy controls were included in the final sample, which was perfectly matched for age, sex (7 female and 11 male), handedness and education. Exclusions among the OCD sample (n=20) were ascribed to image acquisition problems, especially movement (n=8), diagnostic ambiguities (n=2), fMRI task underperformance (n=3), self-report assessment inconsistencies (n=4) and inability to be matched to healthy controls based on age, sex or education (n=3). Conversely, a total of fifteen healthy controls have been excluded due to problems in image acquisition (n=7), subclinical psychiatric diagnosis (n=1), inconsistent self-report responses (n=4), and suboptimal matching (n=3). The Ethics Committee of the Federal University of Rio de Janeiro approved this research protocol. A written informed consent was obtained from all participants. Volunteers were not paid, but received the MRI structural data as an incentive.

A board certified psychiatrist (IF) interviewed all participants with the Structured Clinical Interview for Disorders of Axis I Diagnosis (SCID) (First et al., 1997); the Structured Interview for DSM-IV Personality (SIDP) (Pfohl et al., 1997); the Global Assessment of Functioning Scale (GAF) (Hall, 1995); the Yale-Brown Obsessive-Compulsive Symptom Scale (YBOCS) (Goodman et al., 1989); the Dimensional Obsessive-Compulsive Scale (DOCS) (Abramowitz et al., 2010); and the Detection test of involvement with alcohol,

tobacco and substances (ASSIST) (Humeniuk et al., 2008). The participants also answered the following self-report instruments: the Questionnaire from the Brazilian Association of Population Studies (ABEP) (http://www.abep.org/); the Handedness Questionnaire (Oldfield, 1971); the Beck Depression Inventory (BDI) (Beck et al., 1961).

The inclusion criteria comprised (i) age between 18 and 65 years, (ii) at least high school education, (iii) a minimum score of 16 on the YBOCS for OCD patients, and (iv) a minimum score of 60 on the GAF for controls. The exclusion criteria included Borderline and Antisocial Personality Disorders, alcohol or any substance abuse, increased suicidality (judged to be present on clinical grounds), claustrophobia or any contraindication to the MRI. Almost all OCD patients were medicated with serotonin reuptake inhibitors with the only exception being one subject being treated with a serotonin norepinephrine reuptake inhibitor. Seven patients were also medicated with antipsychotics, six with benzodiazepines, one with a tricyclic antidepressant, one with topiramate and another one with memantine. One Control was medicated with serotonin reuptake inhibitor due to Major Depression in the past however asymptomatic for more than one year.

2.2 - Stimuli and Task

The Moral Sentiments Assessment Task (MSAT) comprised 105 different audio stimuli describing action scenarios ("scripts") designed to evoke four specific emotions (guilt, compassion, anger and disgust) and emotionally neutral social situations; The five different conditions were assessed with 21 scripts each. The current version of the MSAT was based on previous studies(Moll et al., 2007) and previously tested in 20 post-graduate students, who had a correct response rate of approximately 80%.

All scripts were construed with the same two-short sentences grammatical structure. The first sentence described a specific social situation and the second sentence described a

potential volunteers' action coupled with the resulting outcome (e.g., a guilt script: "Your mom called you and said she didn't feel well. You ignored her, and the next day she died"). We instructed participants to put themselves into the specific situation, to imagine themselves as main characters of the specific outcome, and to feel the emotion that the script aroused as vividly as possible. The script had the duration of around 7 seconds and the participants had 5 seconds to do the task. Before the task started, the adequacy of the volume of the audio was individually calibrated.

To test for patients' level of arousal/sleepiness, five seconds after the presentation of a specific script, two circles, one white and one red, appeared side-by-side on randomly alternate sides. The participants were instructed to press the button attached to his right hand to indicate, with his second or third finger, whether the red circle was located on the left or right side of the screen, respectively. The 105 trials, with a 7-second duration each were divided in 3 runs, which took 33.25 minutes in total. After each run, participants were asked if they were feeling comfortable and being able to do the task. There were no significant differences in the arousal reported by OCD patients and controls.

All participants were trained outside the scanner with a Microsoft PowerPoint® presentation that included an example of each of the 5 conditions and the first part of the Positive and Negative Affect Scale (PANAS) (Watson et al., 1988). There were no significant differences between OCD patients and controls in the PANAS positive and negative scores before and after the scan. Higher scores in negative lifetime affects were found in OCD patients as compared to controls.

To ensure that the subjects were attentive and committed to the MSAT, we had them answer the last part of the PANAS and a Recognition Task after the scanning. The recognition task included 45 randomly chosen scripts, fifteen of which were modified.

Subjects were asked to answer whether the script was the same or different from those they heard inside the scanner. To control for the emotions evoked by all the 105 scripts, they also completed a self-report MSAT, in which they had to classify the target emotion of each script with the four emotions plus the neutral category and a "not-able-to-classify" option as possible answers.

INSERT FIGURE 1 HERE

2.3 - Functional MRI data acquisition

Functional images were collected with a 3T Achieva scanner (Philips Medical Systems, the Netherlands) using an eight-channel SENSE head coil. Head motion was restricted with foam pads and straps over the forehead and under the chin. Functional imaging was performed with T2* blood-oxygenation-level-dependent contrast (BOLD) echoplanar imaging (TR/TE = 2000/22 ms); 37 transversal slices were acquired aligned with the anterior-posterior commissure line, positioning the most inferior slice such that temporal lobe was completely covered; slice thickness = 3 mm (no gap); Matrix = 80 X 80, FOV = 240 X 240 mm, flip angle = 90 degrees. High-resolution anatomical images were acquired with a 3D turbo field echo T1-weighted sequence (TR/TE = 7.1/3.4 ms, matrix 240 X 240, FOV 240 mm, slice thickness 1 mm, 170 slices). Per run 345 functional volumes were acquired (excluding the first 5 dummy volumes).

2.4 - Data analysis

Behavioural data analysis was carried out using SPSS (SPSS Inc., Chicago, USA, http://www.spss.com). The fMRI data analysis was performed with SPM 12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Pre-processing steps included

correction for head movement and slice-timing, affine spatial normalization to the EPI template and spatial smoothing (FWHM = 6 mm).

A general linear model (GLM) was applied by performing multiple linear regression of the BOLD response time-course on each voxel, modelling the four emotions (Guilt, Compassion, Anger, and Disgust) plus the neutral conditions with onset directly after the audio script presentation and 5 s duration, and auditory responses with a single regressor for all conditions plus the six movement parameters as nuisance regressors. We excluded any subject due to excessive movement with head dislocation of more than 6 mm (or degrees) in any of the 6 coordinates (x, y, z, pitch, roll, yaw) in a great number of volumes during the exam. Additionally, motion corrected volumes were visually inspected, aided by Artifact Detection Tools (ART) and volumes with excessive movements repaired with our in-house-builded "Denoiser Software" (Mazaika et al., 2005).

We applied a multivoxel pattern analysis (MVPA) with the standard spherical searchlight approach (Bode and Haynes, 2009; Kriegeskorte and Bandettini, 2007; Kriegeskorte et al., 2006) using linear support vector machine (SVM) on the group level (OCD vs. controls). A 9mm radius sphere was employed as the search volume. Four separate searchlight analyses were done using the first-level contrasts (Guilt, Compassion, Anger and Disgust vs. Neutral) as input images. Additionally, we also ran a multiemotion analysis concatenating the four emotional contrasts together as 4D input image, resulting in 4*123=492 features representing a hypersphere in the searchlight.

Every searchlight run was composed of 36 classifications (folds) using a leave-one-subject-out cross-validation scheme. For each fold and each location in the brain mask, we extracted the voxels contained in the searchlight sphere, trained the SVM on 35 subjects and classified the subject left-out for test. The percentage of correct

classifications over the 36 folds was then mapped into the centre of the sphere to create the accuracy maps.

In order to validate statistically our results and to correct for multiple comparisons, we performed permutation testing, following previous recommendations (Stelzer et al., 2013). Exactly the same leave-one-subject-out classification was executed 5000 times, only shuffling the Patient/Control label from the subjects. We used a voxel-wise (cluster-defining) threshold of $p < 0.005$ and $p < 0.05$ to correct for multiple comparison at cluster level, resulting for our data in minimum cluster sizes of 19 voxels in the single condition and 16 voxels for the multi-condition analysis.

An alternative analysis using first level modelling of individual responses to scripts was also performed. In this analysis, all responses not corresponding to the expected "correct" ones based on the normative sample were not modeled (i.e., they were aggregated with null events in the design matrix). The searchlight procedure was identical as described above, but was performed on the first level SPM data using individual responses.

3 - Results

3.1 - Behavioural Data

Our sample was matched for age (in years), education (in years) and socioeconomic status (ABEP scores). Research subjects were also perfectly matched for gender, with seven female and 11 male in each group, given the differences in emotional-processing style by males and females (Wager et al., 2003), four OCD patients and four healthy controls were excluded due to this matching process. No controls had clinically significant depression; on the other hand, six OCD patients had current, seven past and two current and past Major Depressive Disorder. All OCD patients were symptomatic with Y-BOCS obsessions mean score of 13.56 (SD 3.26); Y-BOCS compulsions mean score of 13.94 (SD 2.84) and Y-BOCS total mean score of 27.5 (SD 5.95).

INSERT TABLE 1 HERE

3.2 - Task Data

All subjects included in the final analysis scored 66% or higher in the Red Circle embedded attentional task (three OCD patients were excluded due to poor performance). Also, performance on the recognition task was above 75% in both groups, further indicating that participants were highly engaged in the task and could recall the scripts. Finally, all participants included in the final sample correctly classified scripts according to the independent normative sample, with over 50% accuracy within each emotion condition of the MSAT (four OCD patients and five controls were excluded based on this criterion). The two groups had a matching performance on the MSAT, which was critical for the interpretation of the categorical classification of the fMRI data.

3.3 - fMRI results

3.3.1 - Guilt

The regions that discriminated OCD patients from controls during guilt provocation were the left postcentral and angular gyri, both with an accuracy of 86.1%. For further interpretation of the classification results, we went back to the GLM and built ROIs with the MNI coordinates that resulted from the clusters in searchlight to extract the beta values. These values have the purpose of displaying signal direction; they were not used to compute statistical tests. The extracted beta values from the GLM analysis showed that this classification results were driven by an overall higher activity in the postcentral gyrus of the OCD group and higher activity in the angular gyrus of controls, compared to each other (table 2).

3.3.2 - Compassion

The only discriminative region during compassion provocation was the dorsal anterior cingulate, with an accuracy of 94.4%. The mean beta value in this region was higher in OCD patients compared to controls (table 2).

3.3.3 - Anger

The results from anger provocation showed that multivoxel pattern activity in the caudate nucleus and in the angular, paracingulate and precentral gyri discriminated the OCD and control groups with accuracies of 88.9%, 88.9%, 86.1% and 86.1%, respectively. Mean beta values in the caudate nucleus and paracingulate and precentral gyri were higher in OCD, whereas controls had higher values in the angular gyrus (table 2).

3.3.4 - Disgust

During disgust provocation, the left nucleus accumbens and the medial frontal cortex/ paracingulate gyrus were discriminative between OCD patients and healthy controls, both with an accuracy of 88.9%. Beta values in the left nucleus accumbens were higher in controls, but higher in the medial frontal/paracingulate cortex in OCD patients (table 2).

INSERT TABLE 2 HERE

3.3.5 - Multiemotion analysis

The combined emotion MVPA analysis revealed that the left NAcc, the lingual and middle temporal gyri discriminated OCD from controls with accuracies of 88.9%, 88.9% and 83.3%, respectively. The beta values in the left NAcc and in the middle temporal gyri were higher in controls than in OCD patients. Beta values in the lingual gyrus were higher in OCD patients compared to controls (table 3).

INSERT TABLE 3 HERE

The confirmatory whole-brain searchlight analysis excluding all incorrect hits from the MSAT self-report from the GLM first level analysis of each subject led essentially to the same results, and is therefore not reported herein.

4 - Discussion

In this study, we were able to demonstrate that multivariate decoding of activity in cortical and subcortical regions during the experience of specific moral and non-moral emotions (guilt, compassion, disgust and anger) can accurately discriminate OCD patients from healthy controls. Importantly, activity in some brain regions was particularly accurate in discriminating between groups for a given emotion, whereas other regions contributed to discrimination when analyzed in conjunction. Accuracy of individual regions ranged from 86 to 94%. In addition, we also found brain regions whose dysfunction may not be emotion-specific, but rather implicated in a generalized moral emotions' processing deficit that was also able to differentiate OCD from healthy controls. It should be emphasized that these results derived from cross-validation analyses using permutation methods to empirically estimate statistical effects.

These findings contribute to the emerging body of evidence suggestion a promising role of pattern recognition methods for identifying imaging biomarkers in psychiatric disorders (Sato et al., 2011; 2015); including OCD (For a review, see (Frydman et al., 2016)). It should also be emphasized that the classification results are fundamentally different from conventional fMRI univariate analysis: whereas the multivariate classification tells the accuracy of a given region in distinguishing brain responses, typical fMRI analyses simply shows that the activity of a given region is higher or lower, but does not inform how specific that effects at the single subject level. Our findings thus demonstrate the potential of this approach in identifying moral emotion-related activation patterns in OCD.

In contrast to most recent studies, we have employed a task that reliably elicited both non-moral and moral emotions, both believed to be relevant for OCD psychopathology. Importantly, this multi-emotional task design allowed the selection of a symptomatically

heterogeneous group who were thought to be representative of OCD patients seen in general outpatients' clinics. Our approach also differed substantially from studies employing the passive exposure to pictures that may be actually neutral to healthy controls (such as a doorknob or a toilet seat) and highly aversive for certain OCD patients. Our task and its conditions, in contrast, were carefully designed and tested in order to reliably elicit similar categorizations between OCD and healthy volunteers. The lack of significant behavioral differences in task performance allows us to safely attribute differential fMRI patterns to underlying differences in how their brains respond to equivalent stimuli (at least at the categorical level).

To the best of our knowledge, the only study that employed a similar multivoxel pattern classification strategy (i.e. searchlight) in OCD patients achieved very high accuracies in discriminating functional responses in the orbitofrontal cortex and caudate nucleus during fear-inducing vs. neutral pictures (Weygandt et al., 2012). However, the findings of this previous study are difficult to compare with ours. While the former authors have used a task that included fear, disgust and neutral pictures and pre-defined regions of interest, our task employed a series of auditory stimuli describing rich hypothetical scenarios that reproduce first-person situations and demonstrably elicit non-moral and moral emotions, and a second-level whole-brain multivoxel pattern analysis was employed at the second-level to test the discriminant responses at the whole brain level.

Overall, the former searchlight study and ours concur that the pattern of brain activation in OCD patients can be discriminated from that of healthy controls during experimental emotional elicitation. However, our study further extends these findings by showing that moral sentiments also differ between OCD and controls. Cognitive models suggest that the ability of patients with OCD to tolerate aversive emotions, such as guilt and disgust, may contribute to the maintenance of OCD symptoms (Calkins et al., 2013). Although

exposure and response prevention (ERP), the most effective non-pharmacological treatment for OCD, has generally focused on the confrontation of obsessive fear and anxiety (Marks, 1997), our results suggest that higher-order aversive emotions could also benefit at least some patients with OCD during ERP.

The remarkable discriminative power of the left accumbens activation during disgust provocation and in the multiemotional condition is consistent with existing pathophysiological models of OCD. The NAcc lies at the crossroads of motivation, reward and action (Haber and Knutson, 2010) and has been an effective target for deep brain stimulation in refractory OCD (Kisely et al., 2014). Its activity has been reduced in OCD patients during reward anticipation, particularly in individuals with contamination fears (Figee et al., 2011). Accordingly, we have also found that OCD washers report more positive affect in anticipation of their compulsions than other OCD groups (Ferreira et al., 2017). The findings regarding the discriminative ability of the lingual, middle temporal and angular gyri also dovetail with a model that extends beyond the traditional OCD corticostriatal circuit (Eng et al., 2015; Hu et al., 2016; Jung et al., 2013; Nakao et al., 2014; Piras et al., 2015; Tian et al., 2016; Wood and Ahmari, 2015).

There are some important caveats in our study. Firstly, our OCD sample was relatively small, symptomatically heterogeneous, and under multiple pharmacological treatments. Yet, they were carefully matched and still substantially symptomatic (mean YBOCS score > 27). In addition, the inclusion of OCD patients scoring differently on multiple symptom dimensions (see table 1) was a deliberate research strategy, as subjects were assessed with the MSAT, designed to tap emotions thought to be relevant to the diverse phenomenology of OCD. Secondly, given our emphasis on the searchlight approach and its intrinsic categorical nature, we have not attempted to explore correlations with

severity of OCD symptoms, which would require a larger sample size with a broader range of score variability.

Taken together, our results indicate that (i) the experience of both basic and moral emotions can be effectively decoded from mutivoxel activity patterns in the brain, which can differentiate patients with OCD from healthy controls; (ii) shared or common brain regions, including the nucleus accumbens, lingual gyrus and middle temporal gyrus, are able to discriminate OCD patients from healthy controls across distinct emotions; and (iv) these neural correlates overlap only partially with the frontostriatal circuitry (CSTC), which has traditionally been implicated in OCD pathophysiology. These findings are consistent with the conceptualization of OCD as a brain disorder that involves several different neural circuits. They suggest that current pathophysiological models should incorporate this new evidence, which may also point to new therapeutic targets and purposes. Further studies aiming to establish causality are nevertheless required.

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The authors have nothing to disclose.

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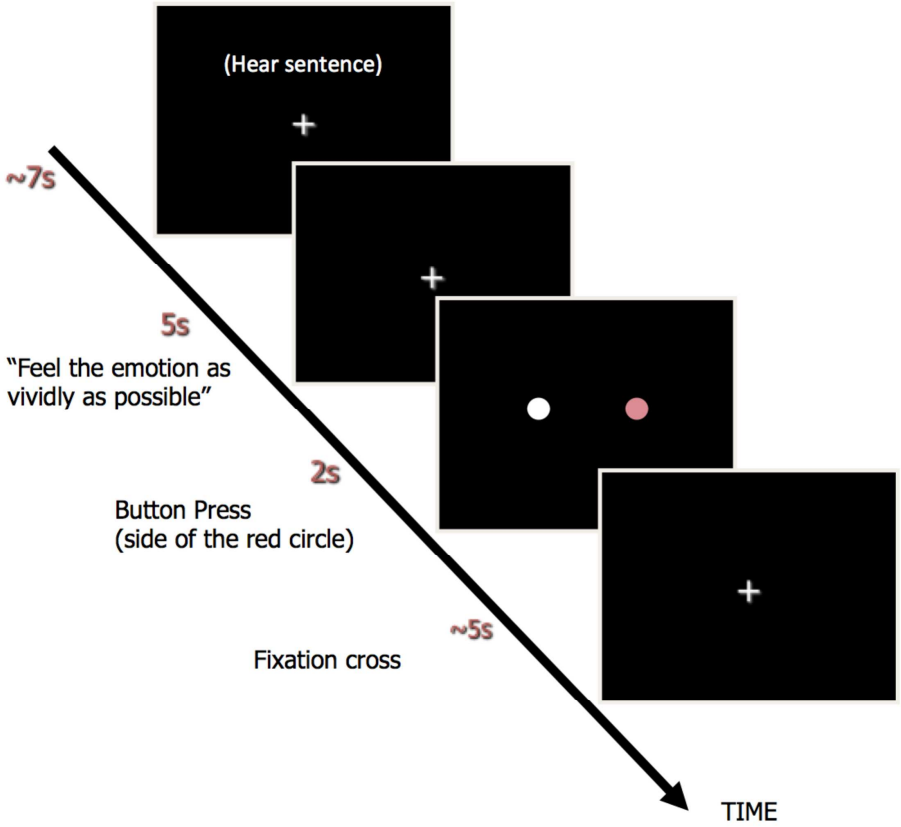

Figure 1: fMRI Task Design.

Table 1 – Sociodemographic characteristics of the sample

	OCD (n=18)	Controls (n=18)	Statistics
Gender			
Female	7	7	
Male	11	11	
Marital Status			$\chi^2 = 1.03$; $p = 0.6$
Single	13	13	
Married	3	4	
Divorced		1	
Age	34.8 (SD 11.5)	32.4 (SD 9.2)	$t = 0.7$; $p = 0.48$
Education	15.17 (SD 1.7)	15.4 (SD 2.5)	$t = -0.3$; $p = 0.76$
GAF	46.4 (SD 8.4)	91.7 (SD 9.2)	$t = -15.4$; $p < 0.001$
BDI	17.65 (SD 8.27)	4.44 (SD 3.3)	$t = 6.3$; $p < 0.001$
ABEP scores	26.44 (SD 10.26)	24.18 (SD 5.8)	$t = 0.8$; $p = 0.43$
DOCS			
Contamination	4.89 (SD 5.29)	.94 (SD .96)	t=3.11; p=.006
Harm	7.94 (SD 6.42)	1.53 (SD 1.94)	t=4.04; p=.001
Taboo	9.89 (SD 6.97)	1.41 (SD 2.18)	t=4.90; p<.001
Symmetry	5.28 (SD 4.77)	.76 (SD 1.20)	t=3.88; p=.001
Total	28.00 (SD 16.21)	4.65 (SD 4.83)	t=5.84; p<.001
Y-BOCS			
Obsessions	13.56 (SD 3.26)	NA	NA
Compulsions	13.94 (SD 2.84)	NA	NA
Total	27.50 (SD 5.95)	NA	NA

OCD = Obsessive-Compulsive Disorder; GAF = Global Assessment of Functioning; BDI = Beck Depression Inventory; ABEP = Brazilian Research Companies Association; DOCS = Dimensional Obsessive-Compulsive Scale; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale; SD = Standard deviation.

Table 2: Searchlight discriminative regions during emotion provocation

	Direction of BOLD effects (beta)	%	MNI coordinates
Guilt			
Postcentral gyrus	OCD > Ctl	86.11%	-57 -55 19
Angular gyrus	OCD < Ctl	86.11%	-39 -34 46
Compassion			
Dorsal anterior cingulate	OCD > Ctl	94.44%	9 35 19
Anger			
Caudate nucleus	OCD > Ctl	88.89%	18 17 19
Angular gyrus	OCD < Ctl	88.89%	-45 -61 22
Paracingulate gyrus	OCD > Ctl	86.11%	0 47 19
Precentral gyrus	OCD > Ctl	86.11%	-36 -16 46
Disgust			
Accumbens	OCD < Ctl	88.89%	-9 14 -8
Medial frontal/ paracingulate cortex	OCD > Ctl	88.89%	18 47 7

OCD = Obsessive-Compulsive Disorder; Ctl = Control; BOLD = Blood-oxygen-level dependent; MNI coordinate = Montreal Neurological Institute coordinate.

Table 3: Searchlight discriminative regions in the multiemotional analysis

Multiemotion	Direction of BOLD effects (beta)	%	MNI coordinates
Accumbens	Ctl > OCD	88.89%	-9 14 -8
Lingual gyrus	OCD > Ctl	88.89%	-12 -76 4
Middle temporal gyrus	Ctl > OCD	83.34%	-57 -61 10

OCD = Obsessive-Compulsive Disorder; Ctl = Control; BOLD = Blood-oxygen-level dependent; MNI coordinate = Montreal Neurological Institute coordinate.

8 - Considerações finais

Iniciei meus estudos tentando entender melhor se existe um fenótipo de início tardio para o TOC, já que não está claro na literatura se o TOC com início tardio seria associado a características mais marcantes. Neste trabalho foram realizadas reflexões em relação ao caminho percorrido para um paciente abrir quadro de TOC em idades mais avançadas da vida do que o habitual, com intuito de tentar identificar uma população de risco. Acredito que este trabalho traduz a dificuldade de se estudar a biologia de um subtipo de TOC, dificuldade esta que pode ser extrapolada para pesquisas em psiquiatria em geral visto a importância da participação de estressores psicossociais, além de outros fatores como acomodação familiar, insight e suporte social.

Nossos resultados sugerem que o TOC tardio tem mais chance de ocorrer em mulheres, indivíduos com períodos mais longos de sintomas obsessivo-compulsivos subclínicos e em associação com um importante evento traumático ocorrido após os 40 anos de idade e história de gravidez na própria pessoa ou em alguém próximo. De fato, mais estudos são necessários, de preferência longitudinais, para promover maior compreensão do assunto. Acreditamos, no entanto, que o trabalho realizado contribuiu para maior discussão do tema e talvez possa guiar próximas pesquisas tentando focar em populações específicas.

No trabalho realizado para o capítulo de livro "Comorbidity in OCSRD" ficou evidente a importância do conceito de comorbidade e de uma doença secundária à outra, de como a comorbidade pode impactar as pesquisas clínicas e a própria prática clínica. A maioria dos pacientes diagnosticados com algum transtorno obsessivo-compulsivo e transtornos relacionados (TOCTR) possuem pelo menos um outro transtorno do DSM-5. As altas taxas de comorbidade podem ser explicados pela neurobiologia subjacente em comum deste grupo.

Por outro lado, as altas taxas podem ser decorrentes de problemas inerentes da classificação diagnóstica em psiquiatria (Maser & Cloninger, 1990). Estamos testemunhando um aumento no número de possíveis diagnósticos nos últimos anos.

As descrições de transtornos específicos realizados pelo DSM tendem a simplificar a complexidade clínica presente em um sujeito ao procurar tratamento.

As altas taxas de comorbidade encontradas nos TOCTR nos levam a questionar se alguns dos transtornos descritos são na realidade sintomas. Quando verificamos na literatura e extrapolando para a vivência na prática clínica algum transtorno que quase sempre não é encontrado sem outro comórbido, fica o questionamento se aquilo não é um sintoma que pode estar presente ou não em diferentes transtornos ou se é um subtipo de outro transtorno. Alucinações auditivas são encontradas em uma gama de diferentes transtornos de diferentes grupos diagnósticos desde transtornos psicóticos a transtornos do humor, por exemplo. Podemos questionar se o transtorno de escoriação e a tricotilomania não seriam sintomas que transpassam diversos transtornos e se a síndrome de referência olfatória não seria um subtipo de transtorno dismórfico corporal.

A reificação de síndromes no DSM, algumas vezes elevadas prematuramente a doenças isoladas, pode levar a uma visão fragmentada do paciente e a propostas terapêuticas não integradas. Clínicos não experientes podem, por exemplo, acreditar que TOC e transtornos de ansiedade são fundamentalmente distintos e comórbidos ao invés de aventar a possibilidade de serem manifestações relacionadas na superfície de síndromes únicas subjacentes (Frances 1990). Não podemos esquecer de adotar uma visão coesa do paciente e de articular o tratamento de diferentes condições de forma coerente considerando o paciente como ser humano único e singular.

Toda essa controvérsia quanto à classificação diagnóstica nos levou a rever a literatura quanto a possibilidade de um neurobiomarcador no TOC no artigo “Can Neuroimaging Provide Reliable Biomarkers For Obsessive-Compulsive Disorder? A Narrative Review”. Desde o advento da ressonância magnética nuclear vemos um número cada vez maior de estudos com inúmeras técnicas e formas de análises diferentes. Esse artigo mostra a complexidade deste tema e como os estudos são heterogêneos, o que dificulta a interpretação dos resultados.

Foi possível confirmar e expandir o papel chave do circuito cortico-estriado-tálamo-cortical (CSTC) e suas conexões límbicas no TOC (Barahona-Corrêa et al., 2015). Por

consequência, foram identificadas estruturas do CSTC que discriminam pacientes com TOC de controles sadios e de transtornos de ansiedade usando estratégias quantitativas (como classificadores) ou qualitativas respectivamente. Já em relação a resposta terapêutica, a espessura do córtex órbito-frontal (OFC) medial direito e esquerdo foi capaz de diferenciar respondedores de não respondedores com uma acurácia em torno de 80% (Hoexter et al., 2015). Talvez no futuro métodos estatísticos de reconhecimento de padrões poderão ser usados na prática clínica. Espera-se que a acurácia seja otimizada combinando métodos simples ou multimodais de imagem com dados clínicos e psicométricos, melhorando nossa capacidade de predizer o curso dos transtornos psiquiátricos (Linden, 2012; Wolfers et al., 2015).

A busca para um biomarcador na psiquiatria associado com alta especificidade e sensibilidade diagnóstica e/ou um bom preditor de resposta (Linden, 2012) se torna complicado a medida que o diagnóstico é definido puramente através de características clínicas como presença de obsessões e compulsões, misturado com comportamentos normais (Mataix-Cols et al., 2003). Desta maneira, a chance de serem neurobiologicamente heterogêneos (como TOC de início precoce e de início tardio) (Fontenelle et al., 2003) e de provavelmente compartilhar de diversas característica diagnósticas (TOCTR) (APA, 2013).

Apesar do progresso da neuroimagem contribuir para uma melhor compreensão dos transtornos psiquiátricos, há também diversos desafios, como por exemplo o fato de diferentes traços biológicos transpassarem saúde e doença. Iniciativas como, do Research Domains Criteria (RDOC), que reconhece muitas dessas barreiras, podem representar um passo a frente em termos de testes diagnósticos na psiquiatria. Como esses avanços podem ser aplicados em uma disciplina essencialmente clinica ainda precisa ser clareado.

Apesar da literatura apontar em um primeiro momento para evidências de traços impulsivos no TOC (Chamberlain et al., 2006; Ettelt et al., 2007; Penadés et al., 2007) e de um modelo de adição comportamental ter sido proposto para o TOC (Fineberg et al., 2010; Fontenelle et al., 2011), o estudo “Subjective and objective impulsivity in obsessive-compulsive disorder“ (submetido no Journal of Behavioral Addiction)

conduzido pelo nosso grupo não corrobora para esses dados. Encontramos que a impulsividade no TOC está restrita ao seu componente subjetivo (particularmente impulsividade atencional) do que testes objetivos. Esses achados sugerem que apesar de se considerarem impulsivos, pacientes adultos com TOC não apresentam evidências objetivas (neuropsicológica) para tal.

Encontramos apenas uma alteração em uma variável (delibaration time) de um dos testes neuropsicológicos usados, o Cambridge Gambling Task (CGT). Esta variável traduz o tempo médio para se escolher uma cor para a caixa, indicando a latência de se realizar uma escolha. Na verdade, fornece uma medida de processamento pre-motor e o tempo de movimento depois que a informação da tomada de decisão é apresentada. Tempo de deliberação prolongado é tradicionalmente correlacionado com danos neurocognitivos encontrados em alcoolistas de longa data e em lesões adquiridas em acidentes (*Cambridge Cognition. All rights reserved. www.cantab.com*, n.d.). Podemos especular que este achado está correlacionado com os sintomas obsessivos-compulsivos que por sua vez pode fazer o sujeito demorar mais tempo para tomar uma decisão.

Quando revisamos com cuidado a literatura dos testes neuropsicológicos no TOC, verificamos que diversos outros estudos também não encontraram evidência de traços impulsivos usando o CGT (Chamberlain, 2007; Chamberlain et al., 2007; 2016; Dittrich and Johansen, 2013). Já em relação o Stop Signal Task (SST), a maioria dos estudos apontam para resposta inibitória comprometida (Boisseau et al., 2012; Chamberlain, 2007; Chamberlain et al., 2006; Penadés et al., 2007). Porém uma metanálise recente mostrou tamanhos de efeito pequeno a médio apenas no tempo de reação do SST (Snyder et al., 2015).

Nossos resultados da impulsividade subjetiva estão de acordo com estudos anteriores que também encontraram pontuação elevada no substrato atencional na Escala de Impulsividade de Barrat (BIS) (Benatti et al., 2014; Boisseau et al., 2012; Ettelt et al., 2007; Grassi et al., 2015). Podemos apontar diferentes aspectos para este achado. Primeiro, temos que considerar que um instrumento de auto-preenchimento é uma medida subjetiva e nos mostra na verdade como o paciente se enxerga.

Já foi encontrado uma correlação entre pontuação elevada do BIS atencional e sintomas sexual, religioso e agressão (Sahmelikoglu Onur et al., 2016). Podemos

especular que dependendo da dimensão que o paciente possui, ele na verdade está com medo de ser impulsivo do que é na realidade, como pacientes com pensamentos de agressão que estão sempre checando se fizeram algo que não queriam ter feito. Talvez para um paciente com TOC o limiar de quão impulsivo uma pessoa pode ser é menor que para sujeitos sem TOC, já que para eles é inaceitável se comportar de forma impulsiva.

Já foi demostrado que não somente pacientes com TOC, mas pacientes com transtornos de ansiedade também possuem pontuação elevada no BIS atencional (Summerfeldt et al., 2004). Foi argumentado que as características principais destes transtornos (evitação de agressão, apreensão ansiosa e preocupação) estão na direção oposta das características da impulsividade. Na verdade, este mesmo padrão de pontuação já foi associado com diferentes transtornos psiquiátricos e parece ser um traço não somente do TOC, mas também da população psiquiátrica em geral (Patton et al., 1995).

No último, mas não menos importante, estudo aqui apresentando "Decoding Moral Emotions in Obsessive-Compulsive Disorder" submetido na Neuroimage: clinical, fomos capazes de demostrar a decodificação multivariada da atividade de regiões corticais e subcorticais durante a experiência de culpa, compaixão, nojo e raiva pode discriminar pacientes com TOC de controles. Importante destacar que a atividade em algumas regiões cerebrais teve acurácia para discriminar os grupos em determinada emoção, enquanto outras regiões contribuíram na discriminação quando as emoções foram analisada em conjunto. Além disso, também encontramos regiões cerebrais que a disfunção não aparenta ser emoção específica, mas sim implicada no déficit do processamento das emoções morais em geral, que também foi capaz de diferenciar pacientes com TOC de controles.

É interessante notar que encontramos regiões cerebrais além do circuito CSTC que discriminaram pacientes com TOC de controles, como o giro lingual, temporal médio e angular. Este achado está de acordo com os estudos mais recentes, sugerindo que outros circuitos cerebrais estão também envolvidos no transtorno independente da tarefa ou método aplicado (Eng et al., 2015; Hu et al., 2016; Nakao et al., 2014; Piras et al., 2015; Tian et al., 2016; Wood and Ahmari, 2015)

Nossa amostra de pacientes com TOC era heterogênea em relação à dimensão de sintomas, com maiores pontuações para blasfêmia e agressão e menores para simetria e contaminação pelo DOCS. Apesar disso, encontramos regiões cerebrais discriminantes entre pacientes com TOC e controles em todas as quatro emoções. Mesmo em nossa amostra com pontuação baixa para contaminação, o nojo parece ser uma emoção importante, por exemplo. Este fato apoia o argumento de que pacientes com TOC processam as emoções de maneira diferente, independente do conteúdo dos sintomas.

Podemos dizer que nosso resultado principal foi encontrar o Núcleo Acumbens (NAcc) Esquerdo como região discriminante entre pacientes com TOC e controle, já que não encontrado apenas durante a provocação de nojo, mas também na análise de Condições Múltiplas (todas emoções juntas). O NAcc junto com o tubérculo olfatório formam o Estriado Ventral, que por sua vez é parte dos Gânglios da Base. O papel do gânglios da base, especialmente do NAcc no sistema de recompensa está bem estabelecido. Porém, o conceito da função dos gânglios da base mudou nos últimos 30 anos de puramente sensório-motor para um muito mais complexo grupo de funções que media comportamentos dirigidos como emoções, motivação e cognição (Haber and Knutson, 2010).

Chama a atenção o fato do NAcc estar hipoativo nos pacientes com TOC. Um estudo encontrou redução na atividade do NAcc em pacientes com TOC comparados com controles durante antecipação de recompensa, especialmente em pacientes com medo de contaminação (Figee et al., 2011). Como o sistema de recompensa está conectado a regiões límbicas, podemos especular que durante a provocação do nojo o NAcc está hipoativo independente da gravidade dos sintomas de contaminação.

O NAcc é um alvo de sucesso da Estimulação Cerebral Profunda (DBS) em pacientes com TOC refratário (Kisely et al., 2014). Além disso, já foi descrito um rebote dos sintomas seguido da interrupção do DBS no NAcc (Ooms et al., 2014). O conceito do DBS é colocar eletrodos de alta frequência estimulando uma região específica do cérebro, porém o mecanismo real da sua ação ainda é desconhecida, se é através de excitação ou inibição (McIntyre et al., 2004; Montgomery and Gale, 2008).

Resumindo, nossos achado indicam que (i) a experiência de emoções morais e básicas podem ser efetivamente decodificada de padrões de atividade de múltiplos “voxel” no

cérebro, que pode ser usado para diferenciar pacientes com TOC de controles; (ii) regiões cerebrais em comum ou compartilhadas, incluindo o NAcc, giro lingual e giro temporal médio, podem discriminar pacientes com TOC de controles independente de diferentes emoções; e (iii) estes correlatos neurais se sobrepõem somente parcialmente com o circuito fronto-estriatal (CSTC) que é implicado tradicionalmente na pato fisiologia do TOC. Esses achados são consistentes com a conceptualização do TOC como um transtorno cerebral que envolve diversos circuitos cerebrais diferentes. Eles sugerem também que o modelo pato fisiológico atual pode ser expandido para incorporar esta nova evidência, que pode apontar para novos objetivos para propostas terapêutica. Mais estudos com o objetivo de estabelecer casualidade são ainda necessários.

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