**UNIVERSIDADE DE SÃO PAULO
FACULDADE DE MEDICINA
DEPARTAMENTO DE PSIQUIATRIA**

FERNANDA VALLE KRIEGER

**Refinando o diagnóstico de Transtorno de Oposição e Desafio na infância e
adolescência: validação e caracterização da dimensão irritável**

Tese apresentada à Faculdade de Medicina
da Universidade de São Paulo para
obtenção do título de Doutor em Ciências

Programa de Psiquiatria

Orientador: Prof. Dr. Guilherme Vanoni Polanczyk

Versão Corrigida

**São Paulo
2015**

Dados Internacionais de Catalogação na Publicação (CIP)

Preparada pela Biblioteca da
Faculdade de Medicina da Universidade de São Paulo

©reprodução autorizada pelo autor

Krieger, Fernanda Valle

Refinando o diagnóstico de transtorno de oposição e desafio na infância e adolescência : validação e caracterização da dimensão irritável / Fernanda Valle Krieger. -- São Paulo, 2015.

Tese(doutorado)--Faculdade de Medicina da Universidade de São Paulo.
Programa de Psiquiatria.

Orientador: Guilherme Vanoni Polanczyk.

Descritores: 1.Humor irritável 2.Transtornos de deficit da atenção e do comportamento disruptivo 3.Herança multifatorial 4.Estudos epidemiológicos 5.Transtornos do humor 6.Sintomas afetivos 7.Emoções

USP/FM/DBD-057/15

AGRADECIMENTOS

Eu só posso agradecer à sorte.

A sorte da vida ter sido tão generosa comigo.

A sorte de ter minha mãe, cujo temperamento, algo irritável é verdade, e o hábito da leitura herdei, e que me ensinou que só o esforço, a dedicação e a persistência nos possibilitam crescer.

A sorte de ter meu pai, que foi o balizador ambiental do meu temperamento e que sistematicamente me mostrou que o processo de aprendizado, crescimento e escolhas envolve uma contemplação quase meditativa.

Aos meus pais, hoje trabalhando exclusivamente com crianças com alterações de comportamento, reconheço a importância de um ambiente continente e que viver com limites fortalece e nos prepara para a vida.

A sorte de ter cruzado durante minha trajetória acadêmica com pessoas tão fora da curva como o Argyris e o Prof. Robert Goodman.

A sorte de ter tido o Guilherme como orientador, que além de também ser fora da curva é absolutamente generoso.

A sorte de ter amigos como o Felipe, meu colega de colégio, meu colega de profissão e meu amigo querido que me recebeu aqui em SP em todas as vindas ao longo destes anos.

E principalmente a sorte de ter reconhecido meu querido e amado André, persona também fora da curva, bondoso, companheiro, amigo e que torna a vida muito mais engraçada e divertida.

Gostaria de agradecer também à Eliza Fukushima e Isabel Ataíde por toda a ajuda durante o doutorado.

Gostaria de agradecer a CAPES por ter me oportunizado o doutorado sanduíche em Londres.

E não poderia deixar de agradecer a toda a equipe do INPD e as crianças que participaram do estudo, sem vocês meu trabalho não seria possível. Muito obrigada!

“Anybody can become angry, that is easy;
but to be angry with the right person, and to
the right degree, and to the right time, and
for the right purpose, and in the right way,
that is not within everybody’s power, that is
not easy.”

Aristóteles (320 A.C.)

NORMALIZAÇÃO ADOTADA

Esta tese está de acordo com as seguintes normas, em vigor no momento desta publicação:

Referências: adaptado de *International Committee of Medical Journals Editors* (Vancouver).

Universidade de São Paulo. Faculdade de Medicina. Divisão de Biblioteca e Documentação. *Guia de apresentação de dissertações, teses e monografias*. Elaborado por Anneliese Carneiro da Cunha, Maria Julia de A. L. Freddi, Maria F. Crestana, Marinalva de Souza Aragão, Suely Campos Cardoso, Valéria Vilhena. 3a ed. São Paulo: Divisão de Biblioteca e Documentação; 2011.

Abreviaturas dos títulos dos periódicos de acordo com *List of Journals Indexed in Index Medicus*.

SUMÁRIO

RESUMO

ABSTRACT

1. INTRODUÇÃO.....	1
2. REVISÃO TEÓRICA.....	4
2.1 Transtorno de Oposição e Desafio.....	5
2.2 Irritabilidade.....	7
2.2.1 Controvérsia acerca da classificação diagnóstica da irritabilidade.....	7
2.2.2 Irritabilidade como um fenótipo dimensional.....	9
2.2.3 Neurobiologia da irritabilidade.....	10
3.OBJETIVOS.....	14
3.1 Objetivo 1.....	14
3.2 Objetivo 2.....	14
3.3 Objetivo 3.....	14
4.HIPÓTESES.....	15
4.1 Hipótese 1.....	15
4.2 Hipótese 2.....	15
4.3 Hipótese 3.....	15
5.PRODUÇÃO CIENTÍFICA.....	16
5.1 Artigo 1.....	17
Irritability in children and adolescents: past concepts, current debates, and future opportunities	
5.1.1 Discussão Artigo 1.....	26
5.2 Artigo 2.....	28
Dimensions of oppositionality in a Brazilian community sample: Testing the DSM-5 proposal and etiological links	
5.2.1 Discussão Artigo 2.....	42
5.3 Artigo 3.....	43
Testing irritability under RDoC framework: evidence from two large and culturally distinct epidemiological samples	
5.3.1 Discussão Artigo 3.....	66

5.4 Artigo 4.....	67
Polygenic score and environmental risk predict irritability in children and adolescents	
5.4.1 Discussão Artigo 4.....	93
6. ANEXOS.....	94
6.1 Artigo 5.....	95
Bipolar disorder and disruptive mood dysregulation in children and adolescents: assessment, diagnosis and treatment	
6.2 Capítulo 1.....	99
Temperament and vulnerability to externalizing behavior	
7. DISCUSSÃO FINAL.....	118
8. CONCLUSÕES FINAIS.....	121
9. REFERÊNCIAS.....	122

RESUMO

Krieger, F. V. *Refinando o diagnóstico de Transtorno de Oposição e Desafio na infância e adolescência: validação e caracterização da dimensão irritável* [Tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2015.

O Transtorno de Oposição e Desafio (TOD) é definido por um padrão recorrente de comportamento desafiante, desobediente e hostil com início na infância e adolescência e caracteriza-se por uma alta taxa de comorbidades. Estudos longitudinais apontam o TOD na infância como um dos principais preditores de psicopatologia na idade adulta. Uma possível explicação para a grande heterogeneidade de comorbidades e trajetórias longitudinais é de que o diagnóstico de TOD abrange distintas dimensões de sintomas, cada qual com seu desfecho. O primeiro objetivo desta tese foi a validação das distintas dimensões do TOD em uma amostra comunitária Brasileira composta de 2512 sujeitos. Através de análise fatorial confirmatória, demonstramos que o modelo que melhor representa a heterogeneidade do TOD é composto por três dimensões: a dimensão “argumentative/defiant” que está associada com transtorno de déficit de atenção/hiperatividade (TDAH); a dimensão “vindictiveness” que possui associação com transtorno de conduta (TC); e a dimensão “angry/irritable mood” onde predominam as associações com transtornos depressivos e de ansiedade. O objetivo seguinte foi investigar o papel da dimensão irritável na classificação nosológica dos transtornos mentais na infância e adolescência. A apresentação da irritabilidade é um aspecto crucial: irritabilidade crônica caracterizada por baixa tolerância à frustração e frequentes explosões de raiva, que é distinta da apresentação episódica, associada ao diagnóstico Transtorno de Humor Bipolar (TB). “Severe mood dysregulation”, “disruptive mood dysregulation disorder”, ou dimensão irritável do TOD são formas distintas de classificar o fenótipo de irritabilidade crônica. Entretanto, independente da classificação utilizada, a alta taxa de comorbidades é invariavelmente o denominador comum em estudos sobre irritabilidade. Neste sentido, examinamos o impacto da irritabilidade como uma dimensão subjacente a vários transtornos. Para tanto, avaliamos o impacto da dimensão irritável do TOD através de vários cenários: indivíduos sem diagnóstico, indivíduos com TDAH e sujeitos com transtornos emocionais. Esta

investigação foi realizada em duas amostras, uma brasileira constituída por 2.512 sujeitos e uma amostra britânica composta de 7.977 sujeitos. Os resultados demonstram que a irritabilidade está associada ao aumento do prejuízo funcional independente do diagnóstico comórbido concomitante. Seguindo esta linha, investigamos a influência genética na etiologia da irritabilidade. Para tanto, criamos um escore poligênico que incluiu polimorfismos associados à baixa tolerância à frustração, raiva, agressividade reativa e labilidade emocional. O escore poligênico foi altamente preditivo dos níveis de irritabilidade em 350 sujeitos da amostra brasileira. A associação foi específica para irritabilidade e não foi significativa para TDAH, TOD ou medidas contínuas de sintomas. Além disso, a influência genética se manteve mesmo quando fatores ambientais foram incluídos no modelo estatístico. Por fim, quando testada em diferentes ambientes, a influência genética na etiologia da irritabilidade foi mais importante em ambientes de alto risco, sugerindo uma correlação gene-ambiente (rGE). Concluindo, nossos resultados sugerem que a irritabilidade se caracteriza como um traço dimensional subjacente a inúmeros transtornos na infância e adolescência e agregando impacto e prejuízo funcional. Neste sentido, o constructo da irritabilidade se enquadra no conceito do “Research Domain Criteria” (RDoC) que propõe o entendimento dos transtornos mentais através de dimensões subjacentes aos diagnósticos clínicos.

Descritores: 1. Humor irritável 2. Transtorno de déficit da atenção e de comportamento disruptivo 3. Herança multifatorial 4. Estudos epidemiológicos 5. Transtornos de humor 6. Sintomas afetivos 7. Emoções

ABSTRACT

Krieger, F. V. *Refining Oppositional Defiant Disorder diagnosis in children and adolescents: validation and characterization of the irritable dimension* [Thesis]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2015.

The Oppositional Defiant Disorder (ODD) is defined as a pattern of disobedient, hostile and defiant behavior beginning in childhood or adolescence and often accompanied by a wide range of comorbidities. Longitudinal studies support ODD as a predictor of psychopathology in adulthood. A potential explanation for such heterogeneity of comorbidities and longitudinal trajectories is that ODD diagnosis encompasses distinct clusters of symptoms, each with its outcome. The first aim of this work was the validation of ODD dimensions in a Brazilian community sample of 2512 subjects. Confirmatory factorial analysis showed that the best model for ODD comprised three dimensions: an “argumentative/defiant” dimension, which associates with attention deficit/hyperactivity disorder (ADHD); a “vindictiveness” dimension, which associates with conduct disorder (CD); and an “angry/irritable” dimension where emotional disorders such as depression and anxiety are the most common associations. The next step was the investigation of the role of the irritable dimension of oppositionality in diagnostic classifications of childhood mental disorders. The pattern of irritability is a crucial point: its chronic presentation as easy annoyance and frequent temper outbursts should be differentiated from the episodic course of irritability associated with the specific diagnosis of Bipolar Disorder (BD). “Severe mood dysregulation”, “disruptive mood dysregulation disorder”, and the irritable dimension of oppositionality are different ways to classify the chronic irritability phenotype. However, regardless of the classification, the high rate of comorbidities is invariably the common denominator in studies of irritability. Therefore, we examined the impact of irritability as a dimension cutting across multiple settings: individuals without any diagnosis, subjects with ADHD, and also those with emotional disorders. For that we used two samples, one from Brazil, with 2.512 subjects, and one from the UK, with 7.977 individuals. Results showed that irritability associates with increased functional impairment regardless of concurrent comorbid status. We then investigated the genetic influence on the etiology of irritability. A polygenic score was generated encompassing polymorphisms

previously associated with anger, emotional lability and reactive aggression. The polygenic score significantly predicted irritability in 350 subjects in the Brazilian sample, yet failed to predict ADHD, ODD, CD and continuous measures of symptoms. Moreover, the association between the polygenic score and irritability remained significant even after taking into account environmental factors. Finally, when stratified across diverse levels of environmental risk, genetic influence upon the etiology of irritability appears to be stronger in high-risk environments. Taken together, our results suggest that irritability is characterized as a dimensional trait that underlies multiple disorders, adding functional impairment. Thus, the construct of irritability fits well within the concept of Research Domain Criteria (RDoC) that suggests that mental disorders should be understood through dimensions underlying diagnostic categories.

Descriptors: 1. Irritable mood 2. Attention deficit and disruptive behavior disorders 3. Multifactorial inheritance 4. Epidemiologic studies 5. Mood disorders 6. Affective symptoms 7. Emotions

1. INTRODUÇÃO

O interesse pelo fenótipo da irritabilidade e pelo diagnóstico de Transtorno de Oposição e Desafio (TOD) surgiu durante a residência em psiquiatria da infância e adolescência no Hospital de Clínicas de Porto Alegre, quando entrei em contato com a alta prevalência desses sintomas e também pelo prejuízo individual e familiar atribuídos a eles. Isso motivou meu estágio opcional no Section on Bipolar Spectrum Disorders, Emotion and Development Branch, no National Institute of Mental Health (NIMH), em Washington/DC, sob supervisão da Dra. Ellen Leibenluft. Nesse período, a controvérsia acerca do papel da irritabilidade na psicopatologia da infância e adolescência estava crescendo e os principais estudos sobre o assunto estavam sendo conduzidos pelo grupo da Dra. Leibenluft no NIMH. Por conseguinte, minha dissertação de mestrado no Programa de Pós-Graduação em Psiquiatria da Universidade Federal do Rio Grande do Sul (UFRGS), sob supervisão do Prof. Luis Rohde, versou sobre o tratamento de crianças com “Severe Mood Dysregulation”, categoria que havia sido recentemente proposta e cujo critério diagnóstico principal era irritabilidade crônica, caracterizada por frequentes crises de raiva, baixa tolerância à frustração e humor predominantemente zangado (1).

A decisão de aprofundar o conhecimento acerca da irritabilidade na infância motivou o desejo de ingressar no curso de doutorado. Coincidentemente, uma parceria entre os grupos de psiquiatria da infância da USP, UFRGS e UNIFESP havia sido contemplado pelo Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) como Instituto Nacional de Ciência e Tecnologia (INCT), o que deu origem ao Instituto Nacional de Psiquiatria do Desenvolvimento (INPD). Além disso, o Prof. Guilherme Polanczyk havia recentemente retornado de pós doutorado no exterior e ingressava como professor no departamento de psiquiatria da USP. Dessa forma, se deu a oportunidade de realizar o doutorado com dados provenientes do primeiro grande estudo epidemiológico em psiquiatria do desenvolvimento conduzido no Brasil, sob supervisão do Prof. Guilherme Polanczyk. Diversas linhas de pesquisa derivaram do INPD, entre eles o Estudo Prevention, cujos dados foram utilizados para a produção dos artigos apresentados nesta tese. O Estudo Prevention teve por objetivo selecionar e acompanhar indivíduos de alto risco para transtornos mentais, definidos através de sintomatologia subclínica e história familiar positiva. A intenção era investigar

marcadores clínicos, neuropsicológicos, genéticos e de neuroimagem estrutural e funcional capazes de prever a conversão de um estado de risco para a síndrome completa, possibilitando assim o planejamento de intervenções preventivas. O estudo foi conduzido em 57 escolas públicas de Porto Alegre e São Paulo e iniciou com a triagem de 9.937 indivíduos de 6 a 12 anos, cujos cuidadores forneceram informações sobre a sintomatologia da criança e também de familiares. As entrevistas foram realizadas predominantemente com a mãe biológica (87.5%), levando em consideração sintomas de 45.394 familiares. A partir dos 9.937 indivíduos que participaram da etapa de triagem, dois métodos de seleção amostral foram realizados. O primeiro utilizou um processo de sobre amostragem priorizando crianças com sintomas subclínicos e/ou história familiar de psicopatologia ($n=1.554$), enquanto o segundo utilizou o processo clássico de seleção aleatória ($n=958$). A amostra final do Estudo Prevention foi composta por 2.512 indivíduos que participaram de extensa avaliação psiquiátrica, neuropsicológica, genética e de imagem (2). As sucessivas etapas do estudo estão ilustradas na Figura 1.

A forma como o Prevention foi estruturado resultou na composição de uma amostra privilegiada de crianças com sintomas subclínicos, facilitando o estudo de fenótipos subsindrômicos, em particular a irritabilidade. A hipótese de que a irritabilidade poderia ser examinada através de uma dimensão subjacente ao diagnóstico de TOD havia sido recentemente proposta, e estava sendo sustentada principalmente por estudos conduzidos pelo Dr. Argyris Stringaris, no Instituto de Psiquiatria da King's College London(3). Este contexto me levou a realizar estágio de doutorado sanduíche por um ano no Departamento de Psiquiatria Infantil do Institute of Psychiatry, King's College London, sob supervisão do Dr. Argyris Stringaris. O período em Londres proporcionou um amadurecimento em relação a todo o processo envolvido na produção científica. O rigor metodológico exigido pelo Dr. Stringaris motivou o estudo de epidemiologia e estatística, e aprendi desde análises estatísticas básicas até complexas modelagens estruturais. Além disso, aprimorei minhas habilidades na redação e estruturação de artigos científicos e tive a oportunidade de acompanhar discussões conceituais relacionadas à pesquisa em psiquiatria do desenvolvimento. Durante o doutorado sanduíche testei a hipótese de distintas dimensões subjacentes ao diagnóstico do TOD utilizando os dados provenientes do Prevention. Este trabalho resultou no artigo publicado no Journal of the American Academy of Child and Adolescent Psychiatry. No

retorno ao Brasil, utilizando paralelamente dados brasileiros e britânicos, examinei o impacto da irritabilidade como um constructo dimensional subjacente a distintas patologias. Por fim, investiguei fatores genéticos e ambientais potencialmente implicados na etiologia da irritabilidade.

Esta tese traz os resultados dessa trajetória de aprendizado que permitiu com que me envolvesse em todas as etapas da produção científica apresentada aqui. Os artigos apresentados refletem sucessivamente o processo de amadurecimento conceitual em relação ao constructo da irritabilidade que ocorreu ao longo dos anos de doutorado.

Figura 1: Fluxograma do Prevention (2)

2. REVISÃO TEÓRICA

O conceito de que os transtornos mentais são possíveis desfechos do desenvolvimento tem sido consolidado por evidências advindas de diferentes áreas do conhecimento (4-7). Estudos epidemiológicos, genéticos e sociais convergem em relação à continuidade do processo de desenvolvimento e os transtornos mentais e que esse processo ocorre a partir de inter-relações complexas e em múltiplos níveis entre características específicas do indivíduo (fatores biológicos, genéticos e psicológicos), características ambientais (cuidado parental, exposição a estressores) e sociais (nível socioeconômico, rede de apoio social)(8-12). O momento no qual essas interações ocorrem parece ser crucial no entendimento do processo psicopatológico, ou seja, interações disfuncionais entre esses vários aspectos podem ter desfechos distintos dependendo da idade do indivíduo (13). Portanto, a identificação de continuidades e descontinuidades do processo de desenvolvimento pode contribuir para o esclarecimento de aspectos relacionados a etiologia, curso e prognóstico dos transtornos mentais (14).

Estudos longitudinais demonstram que existe uma continuidade de sintomas entre a infância, adolescência e idade adulta, e que uma grande proporção de adultos com transtornos mentais já os apresentava na adolescência (15). Dentre os diversos transtornos com início na infância, o Transtorno de Oposição e Desafio (TOD) é apontado como um dos principais precursores de psicopatologia na idade adulta (16, 17). Partindo deste pressuposto, esta tese tem o objetivo de aprofundar e esclarecer os mecanismos pelos quais o diagnóstico do TOD apresenta um perfil de comorbidades tão heterogêneo e prediz distintas trajetórias psicopatológicas. O fenótipo da irritabilidade, que é parte do TOD, está entre as possíveis explicações para o papel central que o transtorno desempenha nos processos psicopatológicos. Consequentemente, esta tese examina especificamente o fenótipo da irritabilidade, seu papel na classificação nosológica atual, investigando suas associações em diferentes cenários, além de seus aspectos etiológicos.

2.1 Transtorno de Oposição e Desafio

O Transtorno de Oposição e Desafio (TOD) foi introduzido como uma categoria diagnóstica distinta pela primeira vez na terceira edição do “Diagnostic and Statistical Manual of Mental Disorders” (DSM-III)(18), sendo definido como um padrão recorrente de comportamento desafiador, desobediente e hostil com início na infância ou adolescência(19).

As estimativas de prevalência do TOD variam entre 2 a 6% em crianças e adolescentes (20-22). Em concordância, estudo de prevalência realizado na cidade de Taubaté, São Paulo/Brasil, identificou o diagnóstico de TOD em 3.2% das crianças em idade escolar(23). A prevalência cumulativa é estimada em 10% e a idade de início dos sintomas ocorre aproximadamente aos 4 anos (24). Em relação à distribuição entre os gêneros, existe uma preponderância do sexo masculino na infância, diferença que tende a desaparecer durante a adolescência onde as taxas entre meninos e meninas são semelhantes (25).

Historicamente o diagnóstico de TOD era considerado uma forma leve ou um precursor de transtorno de conduta (TC). Um critério diagnóstico hierárquico existente até o DSM-IV excluía a possibilidade do diagnóstico de TOD na presença de transtorno de conduta (TC), o que estimulava que os dois diagnósticos fossem estudados em combinado (26, 27). Entretanto, sucessivos estudos demonstraram que apesar de frequentemente comórbidos, os dois diagnósticos deveriam ser considerados constructos independentes(28, 29). A principal razão para a diferenciação entre TOD e TC foram evidências sugerindo que as associações do TOD com aumento de risco para outros transtornos mentais durante a infância e idade adulta ocorriam além e apesar do TC(16, 30).

De fato, a prevalência de TOD em amostras clínicas varia de 30 a 65% e aproximadamente 90% dos indivíduos diagnosticados com TOD apresentam outros diagnósticos ao longo da vida (24). O padrão de comorbidades é heterogêneo e inclui tanto transtornos internalizantes quanto externalizantes. Ao longo da vida as comorbidades concomitantes ao TOD mais frequentes são: transtornos de humor (45.8%), transtornos de ansiedade (62.4%), transtorno de descontrole de impulsos (68.2%) e transtorno de uso de substâncias (47.2%) (24). Por outro lado, dos 5 aos 15

anos, o diagnóstico de TOD está presente em aproximadamente 40% dos sujeitos com qualquer outro diagnóstico segundo o DSM-IV, em 30% dos sujeitos com TDAH e em 20% dos casos com transtornos de ansiedade (20). Diante de taxas tão altas de comorbidades, não surpreende que a presença de TOD aumente sensivelmente o risco (razão de chances) para a ocorrência concomitante de transtornos de ansiedade (odds ratio 7.7), transtornos depressivos (odds ratio 15.1), TDAH (odds ratio 79.0), TC (odds ratio 44.1) e transtorno de abuso de substâncias (odds ratio 4.1) (21, 22).

Estudos longitudinais apontam que o protagonismo do TOD no processo psicopatológico durante a infância e adolescência se estende até a idade adulta (16). Dados oriundos da coorte de Dunedin, estudo prospectivo com início no nascimento e altas taxas de retenção até a idade adulta, demonstram que entre 25 a 60% dos indivíduos com algum transtorno psiquiátrico aos 26 anos possuíam história prévia de TOD. Aos 26 anos, o diagnóstico de TOD durante a infância e/ou adolescência precedia 60% dos casos com transtorno de personalidade antisocial, 40% dos casos de mania (TB), 40% dos sujeitos com esquizofrenia, 38% dos casos com transtorno de abuso de substâncias, 30% dos sujeitos com ansiedade e 25% dos indivíduos com diagnóstico de depressão (17).

Se por um lado os estudos convergiram em relação à importância do diagnóstico de TOD no desenvolvimento do processo psicopatológico, por outro lado evidenciaram a até então pouco explorada complexidade subjacente ao constructo. Doravante, aventou-se a hipótese de que o TOD abrangeria distintas dimensões de sintomas, cada qual com suas associações e trajetórias, mas tendo como denominador comum uma conhecida forma de expressão de sofrimento psíquico na infância: o comportamento disruptivo (31).

Nesta direção, através de análise fatorial exploratória, foram identificadas 3 dimensões subjacentes ao TOD. A primeira dimensão, denominada “Irritable” compreendia os sintomas (i) é raivoso ou ressentido, (ii) descontrola-se com frequência e (iii) é sensível ou facilmente incomodado pelos outros. A segunda dimensão chamada “Headstrong” englobava os sintomas (i) discute com adultos, (ii) ativamente desafia ou se recusa a seguir os pedidos dos adultos ou as regras, (iii) incomoda aos outros de propósito e (iv) culpa os outros pelos seus erros ou má conduta. A terceira dimensão, “Hurtful”, era composta pelo sintoma (i) é malvado ou vingativo(3). Além disso, distintas associações foram descritas para cada dimensão: “Irritable” mostrou-se

particularmente associada com transtornos depressivos e de ansiedade; “Headstrong” foi correlacionada com TDAH e a dimensão “Hurtful” com TC (32). Diferentes modelos de estruturação das dimensões foram propostos, todos com o intuito de aprofundar o conhecimento acerca da heterogeneidade de associações do TOD (28, 33-36).

Recentemente, o DSM-5 contemplou as evidências em relação à heterogeneidade do TOD e incluiu as distintas dimensões como parte do critério diagnóstico para o transtorno. Além disso, o critério hierárquico que excluía a possibilidade do diagnóstico de TOD concomitante ao TC foi extinto. De acordo com o DSM-5 o TOD passou a ser definido como um padrão de “angry/irritable mood”, “argumentative/defiant behavior” or “vindictiveness”(37). Embora as dimensões sejam altamente correlacionadas, atualmente já é possível se estabelecer um padrão predominante de comportamento dentro do diagnóstico de TOD, o que potencialmente viabiliza a predição de trajetórias.

2.2 Irritabilidade

2.2.1 Controvérsia acerca da classificação diagnóstica da irritabilidade

Embora a irritabilidade esteja entre as queixas psiquiátricas mais comuns em crianças e adolescentes, a sua classificação diagnóstica gerou intensa controvérsia nos meios científico e clínico durante a última década. A controvérsia foi desencadeada pelo aumento exponencial no diagnóstico de Transtorno do Humor Bipolar em crianças e adolescentes, observado a partir do final da década de 90(38). As taxas de internação por TB nos Estados Unidos aumentaram de 10 para 34% em crianças e de 10 para 49% em adolescentes num período de 8 anos (39). Em ambientes ambulatoriais, entre 1994 e 2003, o diagnóstico de TB em crianças e adolescentes aumentou 40 vezes, se tornando o mais prevalente nesta faixa etária (40). Estudos examinando a fenomenologia atribuída ao diagnóstico de TB na infância evidenciaram duas características fenotípicas, ambas relacionadas à irritabilidade, eram determinantes no aumento da prevalência. Primeiro, a irritabilidade ao invés de euforia era considerada na maioria das vezes como principal sintoma de humor no diagnóstico de TB em crianças e adolescentes. Segundo, a apresentação dos sintomas (irritabilidade) era considerada predominantemente crônica, ao invés da clássica episodicidade do TB (41, 42). De fato, alguns pesquisadores da área

sustentavam a hipótese de que a irritabilidade representaria uma apresentação fenotípica específica do TB na infância e adolescência (43, 44). Estudos examinando o papel da irritabilidade no diagnóstico de TB na infância demonstraram que o curso da irritabilidade, crônico ou episódico, é o fator de maior relevância diagnóstica (45). O curso episódico, caracterizado por períodos de intensa irritabilidade intercalados com períodos assintomáticos, é associado com mania e com história familiar de TB (46, 47). Por outro lado, o curso crônico, caracterizado por um padrão persistente de irritabilidade se associa com transtornos disruptivos (TDAH e TOD) e depressão (48, 49). Indivíduos com irritabilidade crônica e episódica demonstram estabilidade longitudinal em relação ao seu subtipo, mas diferem em relação ao gênero e idade de início dos sintomas com irritabilidade crônica associando-se ao sexo feminino e menor idade de início(50).

Entretanto, ao mesmo tempo que a distinção entre irritabilidade crônica e episódica delimitou as fronteiras com o diagnóstico de TB, gerou a necessidade de uma classificação diagnóstica específica para a irritabilidade crônica. Pelo menos três formas distintas de classificar irritabilidade crônica foram propostas. “**Severe Mood Dysregulation**” (SMD) caracterizado por excessiva reatividade, frequentes crises de raiva e hipervigilância foi proposto como um fenótipo amplo do TB(51). A pesquisa relativa ao SMD focou principalmente na diferenciação com o fenótipo clássico e episódico do TB(52-54). Em amostra epidemiológica a prevalência de SMD foi estimada em 3.3% e 70% dos casos apresentavam diagnósticos comórbidos, 27% com TDAH, 36% com TC e 25% com TOD(55). Longitudinalmente, SMD foi sistematicamente associado a transtornos de ansiedade e depressivos (56).O refinamento do diagnóstico de SMD, com a exclusão dos sintomas de hipervigilância, deu origem ao “**Disruptive Mood Dysregulation Disorder**” (DMDD), o diagnóstico incluído no DSM-5(37). Existem poucos estudos referentes ao DMDD, o único estudo epidemiológico estimou a prevalência de DMDD entre 0.8 e 3.3%, com um pico nos anos pré-escolares e em meninos. Não surpreende que a principal característica atribuída ao DMDD foi a alta taxa de comorbidades, onde quase a totalidade dos casos apresentaram um segundo diagnóstico. A presença de DMDD aumentou exponencialmente o risco para o diagnóstico concomitante de transtornos depressivos (odds ratio: 9.9 – 23.5) e TOD (odds ratio: 52.9 -103.0). Ou seja, DMDD aumentou em até 100 vezes as chances da ocorrência concomitante de TOD(57). Aos 6 anos a

prevalência de DMDD foi estimada em 8%, e 60% dos casos apresentaram comorbidade com transtornos emocionais e disruptivos. Além disso, nesta faixa etária, DMDD se correlacionou com características de temperamento como excessiva reatividade, pouco controle inibitório e afetividade predominantemente negativa(58). A terceira forma de classificar irritabilidade é através da **dimensão irritável do TOD**, que tem por princípio a apresentação dimensional e cuja definição é compartilhada por temperamentos caracterizados por baixa tolerância à frustração, excessiva reatividade e desregulação emocional (59-62). A maioria das evidências relacionadas à irritabilidade são oriundas de estudos sobre a dimensão irritável do TOD que sistematicamente demonstraram validade preditiva para transtornos depressivos e de ansiedade (63-66).

A sobreposição de desfechos e associações e o aumento na razão de chances (odds ratio) entre as diversas classificações de irritabilidade sugerem que estas categorias são diferentes versões do mesmo fenômeno: crianças com excessiva reatividade, frequentes crises de raiva e baixa tolerância à frustração. Além disso, a alta incidência de diagnósticos comórbidos, sugere a irritabilidade como um constructo subjacente a vários transtornos, e não uma categoria diagnóstica distinta(14).

2.2.2 Irritabilidade como um fenótipo dimensional

Irritabilidade é definida como uma excessiva reatividade a um estímulo emocional negativo, e é descrita como tendo um componente afetivo, geralmente a raiva, e um componente comportamental, a agressividade (67). Reações emocionais são observadas desde os primeiros meses de vida, e inicialmente ocorrem de forma inespecífica e pouco organizada. Progressivamente as manifestações se diferenciam em específicas emoções em determinadas situações. As primeiras manifestações de raiva ocorrem por volta dos 6 meses de idade (68). Entre o primeiro e o terceiro ano de vida, episódios de raiva são frequentes, mas a partir dos 4 anos se espera um declínio na agressividade resultante de um incremento nas competências sociais e no amadurecimento dos mecanismos de auto-regulação, ambos influenciados pelo contexto familiar (69-71). Em torno de 80% das crianças em idade pré-escolar apresentam crises de raiva, entretanto em apenas 8% delas as crises são diárias, imprevisíveis e com duração prolongada, características que sugerem pior prognóstico (72). De fato, temperamentos caracterizados por baixa

tolerância à frustração, desinibição e irritabilidade em pré-escolares predizem uma ampla gama de psicopatologia, particularmente transtornos disruptivos (73, 74). Em idade escolar, raiva e frustração se correlacionam com déficits na auto-regulação e aqueles indivíduos que persistem apresentando crises de raiva ao longo do período escolar são menos flexíveis na interpretação e cumprimento de regras sociais o que interfere diretamente no relacionamento com os pares (75, 76). Pré-adolescentes que apresentam agressividade reativa e impulsiva possuem maior risco para transtornos afetivos e de ansiedade na adolescência (77).

Em síntese, a irritabilidade é um fenótipo dimensionalmente distribuído na população com um pico de incidência nos anos pré-escolares e diminuição progressiva nos anos subsequentes. É durante a infância que trajetórias disfuncionais relacionadas à intensidade e persistência da irritabilidade são delineadas, predispondo esses indivíduos à variadas formas de psicopatologia(78)(79). Estudos longitudinais em amostras comunitárias demonstram que irritabilidade na infância está associada com transtornos disruptivos, particularmente TDAH, na adolescência e com transtornos depressivos e de ansiedade na idade adulta (55, 80, 81). Dentro de uma perspectiva dimensional, as classificações diagnósticas descritas anteriormente (SMD e DMDD) representariam o extremo superior da curva.

2.2.3 Neurobiologia da irritabilidade

Embora existam poucos dados sobre a neurobiologia da irritabilidade, a definição do fenótipo como uma propensão a sentir raiva e reagir com agressividade diante de um estímulo emocional negativo, sugere a participação de dois sistemas no processo psicopatológico. O primeiro sistema, denominado “bottom-up” é composto por estruturas subcorticais que são responsáveis por emoções básicas, por exemplo a raiva e a agressividade. O segundo sistema, denominado “top-down” é composto por estruturas do córtex pré-frontais e envolve mecanismos cognitivos responsáveis pelo controle inibitório e processamento de informações advindas de estruturas mais primitivas, o que permite o planejamento das ações. Portanto, a neurobiologia da irritabilidade abrange circuitarias e estruturas cerebrais implicadas nos sistemas “bottom-up” e “top-down” e a interação que ocorre entre eles (82).

“Bottom-up system”

O sistema *‘bottom-up’* tem origem ancestral e é composto por estruturas cerebrais subcorticais que se mantiveram intactas ao longo do processo de evolução das espécies. Por ser comum à distintas espécies animais, sugere-se que essas áreas são responsáveis pela formação dos sentimentos e instintos mais primitivos. De fato, compartilhamos emoções básicas como a raiva e o medo com espécies muito menos evoluídas do ponto de vista cognitivo, o que corrobora a hipótese de que afetos e estados emocionais que constituem a mente afetiva primitiva tem origem abaixo do “capacete do pensamento” neocortical (83).

A raiva é considerada uma emoção básica e sua circuitaria inicia em regiões subcorticais profundas e específicas da substância cinzenta periaquedutal, passando pela porção medial do hipotálamo e superficializando em áreas mediais da amígdala(84). Estes circuitos foram testados em outros mamíferos, e a raiva pode ser evocada mediante a estimulação elétrica destas regiões. A circuitaria da raiva está organizada de forma hierárquica, onde estruturas mais profundas são mais importantes na geração de comportamentos agressivos. Por exemplo, a raiva provocada no sistema periaquedutal não é influenciada por lesões nas regiões mediais do hipotálamo e amígdala. Por outro lado, lesões na substância cinzenta periaquedutal praticamente eliminam a raiva evocada na amígdala. Estudos de imagem relacionados à raiva são escassos, pois tendem a ser menos ilustrativos em regiões subcorticais. Além disso, diante da evocação da raiva, mecanismos inibitórios e regulatórios corticais são acionados numa tentativa de conter a emoção básica, tornando difícil o discernimento entre o mecanismo básico da raiva e mecanismos compensatórios. Entretanto, estudo usando tomografia por emissão de pósitrons (“PET CT”) identificou um aumento do fluxo sanguíneo em áreas profundas mediais onde se localiza o sistema periaquedutal, considerado o epicentro da emocionalidade, além de áreas adjacentes como o locus coeruleus responsável pela vigilância cerebral (“arousal”)(85).

Enquanto a substância cinzenta periaquedutal é crucial na geração da raiva, a amígdala parece ser mais relevante nas relações com estruturas cognitivas que desencadeiam o processo instintivo da raiva(86). Um dos mecanismos atribuídos à excessiva irritabilidade deriva justamente da informação advinda de regiões corticais que é comunicada através da amígdala às estruturas subcorticais, desencadeando consequentemente a reação agressiva. É importante observar, que apesar de primitivas,

as reações subcorticais geralmente tem um significado, ou seja, um fator desencadeante que explica a intensidade do impulso agressivo(84). Evidências sugerem que crianças e adolescentes com níveis elevados de irritabilidade apresentam uma tendência a perceber estímulos neutros como hostis. Portanto, diante da percepção errônea de ameaça iminente, tendem a reagir de forma acentuada(87)(76). Essa distorção na interpretação de estímulos neutros como ameaçadores é uma possível explicação para a associação entre irritabilidade e transtornos de ansiedade.

“Top-down system”

O sistema “top-down” é composto por estruturas do córtex pré-frontal e regiões adjacentes, e está diretamente envolvido regulação emocional através de um conjunto de processos cognitivos conhecidos como funções executivas. As funções executivas são processos cognitivos sofisticados que atuam com o objetivo de proporcionar ao indivíduo atingir um comportamento desejado ou permitir que um objetivo seja alcançado (88). Mecanismos cognitivos complexos tais como a capacidade de inibir uma resposta inapropriada a um determinado estímulo (controle inibitório), a capacidade de pensar estrategicamente (memória operacional), o planejamento e a previsão de consequências que incluem recompensas e punições fazem parte das funções executivas, e consequentemente são importantes no processo de regulação emocional (89). A regulação emocional é necessária quando o estado emocional do indivíduo diverge do que é esperado em determinada situação e tem por objetivo minimizar danos conduzindo o sistema emocional em uma direção mais vantajosa. A mudança na direção do estado emocional é atingida através de mecanismos cognitivos que incluem mudanças na direção da atenção (região ventrolateral do córtex pré-frontal), reavaliação e reinterpretação da situação e de possíveis consequências (88).

Em indivíduos irritados, existe uma tendência a experienciar raiva diante da frustração, o que caracteriza um prejuízo na regulação emocional, já que a raiva frequentemente seguida de agressividade parece não ser a resposta mais vantajosa nessa situação. Uma das estratégias na busca de respostas mais adaptativas diante da frustração consiste na supressão da expressão emocional através do controle inibitório que ocorre em regiões do córtex pré-frontal (90). O prejuízo no controle inibitório está associado ao aumento da frustração e da agressividade reativa (84), além de estar intimamente relacionado a impulsividade (91). Em comparação, estratégias que incluem flexibilidade cognitiva e reavaliação ou ressignificação (“reappraisal”) do estímulo

emocional parecem ser uma das formas mais efetivas de diminuir o impacto negativo decorrente do evento aversivo (92). O efeito da ressignificação é resultado de interações entre processos de controle cognitivo (córtex pré-frontal orbital e cíngulo anterior) e regiões responsáveis pela avaliação e interpretação das emoções, por exemplo a amígdala (86). O uso de ressignificação na modulação de emoções negativas diminui a atividade da amígdala, diminuindo assim a “comunicação” com as descritas estruturas subcorticais, geradoras do impulso agressivo(93). Estudos medindo flexibilidade cognitiva demonstraram que indivíduos com irritabilidade ativam menos a região ventrolateral do córtex pré-frontal, que está associada a mudanças na direção da atenção, o que facilitaria a inibição de uma resposta preponderante e a execução de uma alternativa(94)(95).

3.OBJETIVOS

3.1 Objetivo 1

O primeiro objetivo desta tese foi investigar as dimensões do Transtorno de Oposição e Desafio (TOD) em uma população brasileira, validando a irritabilidade como uma dimensão distinta.

3.2. Objetivo 2

O segundo objetivo desta tese examinou a irritabilidade como um constructo dimensional subjacente a múltiplos processos patológicos, investigando sua validade preditiva em distintas situações clínicas em duas amostras epidemiológicas, uma brasileira e uma britânica.

3.3 Objetivo 3

O terceiro objetivo desta tese foi investigar a influência genética e ambiental na etiologia da irritabilidade.

4. HIPÓTESES

4.1 Hipótese 1

A primeira hipótese desta tese sugere a replicação das dimensões do TOD em uma amostra brasileira, possibilitando a validação da irritabilidade como uma dimensão distinta.

4.2 Hipótese 2

A segunda hipótese sugere que a validade preditiva da dimensão irritável é similar em distintas situações clínicas, ou seja que a dimensão irritável está associada a um aumento do prejuízo funcional independentemente do diagnóstico comórbido concomitante e que os achados são similares em amostras culturalmente distintas.

4.3 Hipótese 3

A terceira hipótese propõe que a etiologia da irritabilidade está associada a aspectos genéticos (derivados de um escore poligênico) e ambientais previamente associados a aspectos inespecíficos de regulação emocional e baixa tolerância à frustração.

5. PRODUÇÃO CIENTÍFICA

5.1 Artigo 1

Irritability in children and adolescents: past concepts, current debates, and future opportunities

5.2 Artigo 2

Dimensions of oppositionality in a brazilian community sample: testing the DSM-5 proposal and etiological links

5.3 Artigo 3

Testing irritability under RDoC framework: evidence from two large and culturally distinct epidemiological samples

5.4 Artigo 4

Polygenic score and environmental risk predict irritability in children and adolescents

5.1 Artigo 1

“Irritability in children and adolescents: past concepts, current debates, and future opportunities”

UPDATE ARTICLE

Irritability in children and adolescents: past concepts, current debates, and future opportunities

Fernanda Valle Krieger,^{1,2,3} Ellen Leibenluft,⁴ Argyris Stringaris,³ Guilherme V. Polanczyk^{1,2,5}

¹Department of Psychiatry, Universidade de São Paulo (USP), São Paulo, SP, Brazil. ²National Science and Technology Institute for Developmental Psychiatry for Children and Adolescents (INCT), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

³Institute of Psychiatry, King's College London, London, UK. ⁴Emotion & Development Branch, National Institute of Mental Health (NIMH), Department of Health and Human Services (HHS), USA. ⁵Department of Psychiatry, Medical School and Research Support Center on Neurodevelopment and Mental Health, USP, São Paulo, SP, Brazil.

Irritability is defined as a low threshold to experience anger in response to frustration. It is one of the most common symptoms in youth and is part of the clinical presentation of several disorders. Irritability can present early in life and is a predictor of long-term psychopathology; yet, the diagnostic status of irritability is a matter of intense debate. In the present article, we address two main components of the debate regarding irritability in youth: the misdiagnosis of chronic irritability as pediatric bipolar disorder, and the proposal of a new diagnosis in the DSM-5, disruptive mood dysregulation disorder, whose defining symptoms are chronic irritability and temper outbursts.

Keywords: Irritability; disruptive behavior; mood; dysregulation; children; adolescents

Introduction

Irritability is defined as a low threshold to experience anger in response to frustration. It is one of the most common symptoms in youth and is part of the clinical presentation of several disorders. Irritability can present early in life and is a predictor of long-term psychosocial adversity; yet, the diagnostic status of irritability is a matter of intense debate.¹ In the present article, we present a review of two aspects of irritability in children and adolescents: 1) The historical and theoretical background of the debate regarding the association of irritability with youth bipolar disorder (BD) and its role in the dramatic increase in the rates of this disorder reported in recent years; 2) The proposal of a new diagnostic category in the DSM-5 called disruptive mood dysregulation disorder (DMDD), with chronic irritability and temper outbursts as the defining symptoms. Because the conceptualization of this entity is a work in progress, we reviewed up-to-date clinical and epidemiological data on DMDD.

The controversy about irritability and youth bipolar diagnosis

Mental disorders are the result of maladaptive trajectories throughout development.² Approximately 80% of adult mental disorders begin during childhood and adolescence. In some cases, the same disorder is found in different stages of development (homotypic continuity); whereas in others the clinical phenotype changes with

development (heterotypic continuity).³ In recent years, researchers have focused on identifying the developmental trajectories of psychopathology, in the hope that this could help clarify relevant aspects of etiology, course, prognosis, prevention, and therapeutic strategies.⁴ BD is a mood disorder that causes high levels of functional impairment. Retrospective studies showed that in 50% of cases BD begins during adolescence. Therefore, the developmental trajectory of BD is of great interest for researchers and clinicians.⁵

Between the mid 1990s and early 2000s in the United States, there was a dramatic increase in the rate of diagnosis of BD in children and adolescents, paralleling a discussion in the professional literature about the presentation of BD in youth.⁶ The proportion of bipolar diagnosis of all psychiatric inpatient discharges in the United States rose from 10 to 34% in children and from 10 to 49% in adolescents in 8 years. In 1996, there were 1.3 discharges with a bipolar diagnosis per 10,000 children and adolescents in the general population, whereas in 2004 the ratio was 7.3 per 10,000, a five-fold increase. In outpatient settings, the increase was approximately 40-fold during that period.⁷ It is possible that youth BD was previously underdiagnosed, explaining the increase in the rates. However, another plausible explanation is a change in the way the diagnostic criteria were applied, leading to misdiagnosis of other conditions under the label of BD.

BD is characterized by episodes of mania or hypomania, i.e., a distinct period of abnormally and persistently elevated, expansive, or irritable mood (A symptoms) accompanied by a number of cognitive, behavioral, and physical symptoms (B symptoms) such as grandiosity, decreased need for sleep, pressure of speech, increased

Correspondence: Fernanda Valle Krieger, Instituto de Psiquiatria, Universidade de São Paulo, Rua Dr. Ovídio Pires Campos, 785, 1º andar, sala 1C015, CEP 05403-903, São Paulo, SP, Brazil.
E-mail: fvkrieger@gmail.com

goal-directed activities, flight of ideas, distractibility, and psychomotor agitation. The concurrent presence of A and B symptoms configures an episode of mania or hypomania; the difference between the two depends on the intensity and duration of symptoms.⁸ Specifically, the controversy in pediatric BD was focused on chronic, nonepisodic irritability as a developmental presentation of BD.⁹ Although the core definition of BD comprises an episode, some researchers have suggested that mania in youth presents as a nonepisodic, persistent, chronic, and severe irritability.¹⁰⁻¹² This shift in the concept of bipolar illness has obvious implications in nosological classification, prevalence, therapeutic approaches, and prognosis. For instance, accepting youth BD as chronic and nonepisodic leads to overlap of symptoms with other disorders. For instance, distractibility, increased goal-directed activities, pressure of speech, and psychomotor agitation occur both in mania and attention deficit hyperactivity disorder (ADHD). The episodicity of the presentation was useful to differentiate BD and ADHD, because while irritability is not a diagnostic criterion for ADHD, temper outbursts and deficits in emotional regulation (chronic irritability) are often seen in this entity. Thus, defining BD in youth as chronic may then result in many children with ADHD and irritability receiving the diagnosis of BD, increasing the rates of comorbidity. Therefore, the nonepisodic hypothesis of youth BD kindled interest and concern among researchers, stimulating research in the field.¹³

The considerations above show that the presentation of irritability - chronic or episodic - is crucial for understanding its psychopathological meaning, particularly because the constructs of episodic and chronic irritability are separable and remain stable over time.¹⁴ For instance, the correlation of episodic irritability between early and late adolescence is 0.79, whereas that of chronic irritability, is 0.56. However, the correlation between episodic and chronic irritability is much lower, 0.34 in early and 0.26 in late adolescence.¹⁵ Thus, chronic and episodic irritability seldom overlap but are each relatively stable over time. Furthermore, the two constructs present different associations with age: episodic irritability has a linear association, whereas chronic irritability presents a curvilinear trajectory, with a peak in mid-adolescence. In addition, longitudinal associations are also diverse between the two phenotypes: episodic irritability in early adolescence is associated with generalized anxiety disorder (GAD), simple phobia, and mania in late adolescence and only mania in early adulthood, whereas chronic irritability in early adolescence is associated with disruptive disorders in late adolescence and only with major depressive disorder (MDD) in early adulthood.¹⁵

In 2003, Leibenluft et al. proposed a systematization of critical aspects of the youth bipolar debate, thus prompting research on the field¹⁶: 1) narrow phenotype, including those patients who meet the full DSM-IV diagnostic criteria for (hypo)mania, with hallmark symptoms of elevated mood and duration criterion (7 days for mania; 4 days for hypomania); 2) (hypo)mania not

otherwise specified, featuring those who exhibit clear episodes with elation as the hallmark symptom, but duration between 1-3 days; 3) irritable (hypo)mania, in which patients have a clear episode with irritability but not elated mood as the main symptom; and 4) broad phenotype, also called severe mood dysregulation (SMD), characterized by chronic, nonepisodic illness, and severe irritability.

Since then, several studies have established differences between the classical episodic bipolar phenotype (BD) and those exhibiting chronic irritability and temper outbursts (SMD). Whereas both groups show similar levels of impairment on the Children's Global Assessment Scale (BD 51.1 ± 10 ; SMD 47.4 ± 9 , both indicating moderate impairment), the BD group presents higher rates of familial BD.¹⁷ To address the issue of whether children with SMD would develop episodes of mania, longitudinal analyses have been conducted. Irritability in adolescence predicted MDD (odds ratio [OR] = 1.33, 95% confidence interval [95%CI] 1-1.78), generalized anxiety disorder (OR = 1.72, 95%CI 1.04-2.87), and dysthymia (OR = 1.81, 95%CI 1.06-3.12). Youth irritability did not predict BD at follow-up.¹⁸ Conversely, those with classical BD, including an episodic course and elated mood, had up to 50 times more chance to develop a manic episode than those with SMD (i.e., chronic irritability) in a three-year follow-up (BD 58/93 subjects - 62%; SMD 1/84 subjects - 1.2%).¹⁹ In addition, neuropsychological and imaging data gave further contributions to the differentiation between BD and chronic irritability.²⁰⁻²²

In short, there is definite evidence for a well-circumscribed entity characterized by episodic elated and/or irritable mood and well-defined associated symptoms that can be diagnosed as BD.²³ This entity needs to be identified clearly and treated appropriately because of a high probability of poor outcomes throughout life.²⁴ Conversely, patients identified as having chronic irritability should not be treated as exhibiting a developmental manifestation of BD. Because the goal of this review is pediatric irritability, we now move from the controversy surrounding BD to focus on data addressing specifically chronic irritability and emotional dysregulation in children. We characterize clinical pictures whose main symptoms are persistent irritability and temper outbursts that are impairing in both the short and long term. We also discuss functional burden, family history, neuropsychological findings, and nosological uncertainties. We conclude addressing therapeutic strategies.

Chronic irritability, temper outbursts, and disruptive mood dysregulation disorder

Irritability is defined as above, i.e., a deficit in emotional regulation. Developmentally appropriate anger-related behaviors tend to reflect frustration in expectable contexts, whereas chronic irritability is inappropriate to the situation, i.e., stimuli that could be manageable elicit intense responses manifested by reactive verbal and/or physical aggression towards the perceived object of threat or frustration. Deficits in emotional regulation are

highly associated with psychopathology and one of the most important predictors of mental disorders in cross-sectional and longitudinal studies.²⁵ Despite the impact of emotional dysregulation on child and adolescent psychopathology, it has no definite nosological home in the current classificatory systems. Some efforts have been made, but the phenotypic presentation of impairing emotional dysregulation is still open and is an empirical question. Currently, there are at least four different ways to classify this group of children.

Firstly, SMD was proposed as a phenotypic differentiation from BD. The diagnostic criteria comprised abnormal mood (anger or sad, at least half of the day, most days), frequent temper outbursts (three times/week), and

hyperarousal symptoms (three or more: insomnia, agitation, distractibility, racing thoughts or flight of ideas, pressured speech, and intrusiveness). Symptoms must cause severe impairment in one setting (i.e., home, school, peers) and mild impairment in a second setting, must begin before 12 years of age and be present for at least 12 months, without symptom-free periods exceeding 2 months (Table 1). The research on SMD focused on the differentiation from BD, and neuropsychological and imaging data comparing the two entities clarified its boundaries.^{26,27} Furthermore, research on SMD stressed the importance of chronic irritability for developmental psychiatry and suggested its adoption by the DSM-5. In an epidemiological sample, lifetime prevalence for SMD

Table 1 Diagnostic criteria: SMD vs. DMDD

SMD	DMDD
1. Compared to his/her peers, the child exhibits markedly increased reactivity to negative emotional stimuli that is manifest verbally or behaviorally. For example, the child responds to frustration with extended temper tantrums (inappropriate for age and/or precipitating event), verbal rages, and/or aggression toward people or property. Such events occur, on average, at least three times a week.	A. The disorder is characterized by severe recurrent temper outbursts that are grossly out of proportion in intensity or duration to the situation. <ol style="list-style-type: none"> 1. The temper outbursts are manifest verbally and/or behaviorally, such as in the form of verbal rages or physical aggression towards people or property. 2. The temper outbursts are inconsistent with developmental level.
2. Hyperarousal, as defined by at least three of the following symptoms: insomnia, agitation, distractibility, racing thoughts or flight of ideas, pressured speech, intrusiveness.	B. Frequency: the temper outbursts occur, on average, three or more times per week.
3. Abnormal mood (specifically anger or sadness), present at least half of the day most days, and of sufficient severity to be noticeable by people in the child's environment (e.g., parents, teachers, peers).	C. Mood between temper outbursts: <ol style="list-style-type: none"> 1. Nearly every day, most of the day, the mood between temper outbursts is persistently irritable or angry. 2. The irritable or angry mood is observable by others (e.g., parents, teachers, peers).
4. The symptoms noted in 2-4 above are currently present and have been present for at least 12 months without any symptom-free periods exceeding 2 months.	D. Duration: criteria A-C have been present for 12 or more months. Throughout that time, the person has not had 3 or more consecutive months without the symptoms of criteria A-C.
5. The symptoms are severe in at least one setting (i.e., violent outbursts, assaultiveness at home, school, or with peers). In addition, there are at least mild symptoms (distractibility, intrusiveness) in a second setting.	E. Criterion A or C is present in at least two settings (at home, at school, or with peers) and must be severe in at least one setting.
6. Aged 7-17, with the onset of symptoms before age 12.	F. The diagnosis should not be made for the first time before age 6 or after age 18.
	G. The onset of criteria A through E is before age 10.
	H. There has never been a distinct period lasting more than one day during which abnormally elevated or expansive mood was present most of the day, and the abnormally elevated or expansive mood was accompanied by the onset, or worsening, of the three of the B criteria of mania (i.e., grandiosity or inflated self-esteem, decreased need for sleep, pressured speech, flight of ideas, distractibility, increase in goal directed activity, or excessive involvement in activities with a high potential for painful consequences). Abnormally elevated mood should be differentiated from developmentally appropriate mood elevation, such as occurs in the context of a highly positive event or its anticipation.
	I. The behaviors do not occur exclusively during an episode of major depressive disorder and are not better accounted for by another mental disorder (e.g., autism spectrum disorder, posttraumatic stress disorder, separation anxiety disorder, dysthymic disorder). [*] The symptoms are not due to the effects of a drug or to a general medical or neurological condition.

DMDD = disruptive mood dysregulation disorder; SMD = severe mood dysregulation.

^{*} Note: This diagnosis cannot co-exist with oppositional defiant disorder or bipolar disorder, though it can co-exist with attention deficit hyperactivity disorder and substance use disorders. Individuals meeting criteria for both DMDD and oppositional defiant disorder should only be given the diagnosis of DMDD. If an individual has ever experienced a manic or hypomanic episode, the diagnosis of DMDD should not be assigned.

was 3.3%. Around 70% of SMD youth had a concomitant axis I diagnosis, ADHD (27%), conduct disorder (CD) (36%), and oppositional defiant disorder (ODD) (25%). Moreover, those who met criteria for SMD at first wave (mean age 10.6 ± 1.4 years) were significantly more likely to be diagnosed with a depressive disorder (OR = 7.2, 95%CI 1.3-38.8) at follow-up (mean age 18.3 ± 2.1 years) than youth who never met criteria for SMD.²⁸

Secondly, the DSM-5 working group excluded the hyperarousal criterion from SMD, since it overlapped with ADHD symptoms,²⁹ and proposed a new diagnostic category called DMDD (Table 1). There is still little evidence on DMDD and studies mostly construct the phenotype based on other DSM-IV symptoms. Recently, Copeland et al., using two community samples, suggested prevalence rates of DMDD between 0.8 to 3.3%, with higher rates in preschool aged and male individuals. In the same study, DMDD significantly co-occurred with all common psychiatric disorders. The highest levels of co-occurrence were with depressive disorders (OR between 9.9 and 23.5) and ODD (OR between 52.9 and 103.0). Only one case of DMDD overlapped with mania. The likelihood of DMDD occurring alone ranged from 8% to 38% (for comparison, conduct disorder occurred alone 64% of the time, and depression occurred alone in 36.6%). Besides, youth with DMDD experienced higher levels of all social impairments and had elevated rates of recent suspension compared with those without DMDD criterion. These individuals were more likely to come from impoverished families.³⁰

In another study with a clinically referred sample - $n=706$, aged 6-12 years, who participated in the Longitudinal Assessment of Manic Symptoms (LAMS) - high levels of overlap with other disorders were also described.³¹ At intake, the DMDD phenotype was present in 26% of patients. Nearly all subjects with DMDD (96%) met criteria for ODD/CD and 77% met criteria for both ODD and ADHD. Compared with those without the phenotype, DMDD subjects presented higher rates of disruptive behavior disorders, dysthymia, and ADHD as well as higher scores on Young Mania Rating Scale (YMRS), Children Depression Rating Scale (CDRS), and ODD and CD subscales of the Child and Adolescent Symptom Inventory. At a 12-month follow-up, only 53% of those meeting criteria for DMDD at intake continued to meet criteria. Of those meeting criteria at any assessment (intake, 12-month, and 24-month follow-up), 52% did it at only one assessment, 30% at two, and 20% at all three time points. A diagnosis of DMDD at any time-point was significantly associated with a diagnosis of ODD/CD (71% of those with ODD also had DMDD vs. 3% without ODD, $p < 0.0001$) and ADHD (44% of those with ADHD also had DMDD vs. 23% without ADHD, $p < 0.0001$), but there was no association with any depressive disorder, any anxiety disorder, or BD. There was no specific association between DMDD and family history of mental disorders. The authors concluded that the DMDD phenotype could not be clearly delimited from ODD and CD and it showed limited longitudinal diagnostic stability.

Thirdly, the Irritable dimension within the ODD diagnosis is characterized by temper outbursts, annoyance, and touchiness.³² Similar to SMD, the Irritable dimension shows strong association with emotionality.^{33,34} However, even though both share the same core features, the assumption of SMD/DMDD as a specifier of ODD (Irritable dimension) was considered insufficient to describe the phenotype clinically. The DSM-5 Task Force argued that a syndrome characterized by chronic irritability, temper outbursts, and association with depressive disorders should be labelled under a mood section rather than a section on disruptive disorders, like ODD. In a British sample, the Irritable dimension of ODD was the only predictor of emotional disorders (anxiety and/or depression) compared to the other ODD dimensions of oppositionality, headstrong, and hurtful.³² The association between Irritable dimension of ODD and internalizing disorders was replicated in distinct samples and age groups.³⁵⁻³⁷ Longitudinal data from the British national survey ($n=7,912$) showed that the Irritable dimension of ODD predicted emotional disorders at follow-up, particularly distress disorders (depression and anxiety).¹⁸ Findings of shared genes between the Irritable dimension of ODD and depressive disorders provided further support of a developmental association between them.³⁸ Moreover, the Irritable dimension of ODD showed a strong association with maternal depression.³⁹ The DSM-5 subtyped ODD into three dimensions (1. Angry/Irritable Mood; 2. Argumentative/Defiant Behavior; 3. Vindictiveness),³² excluding the possibility of comorbidity between DMDD and ODD. If ODD and DMDD co-occur, DMDD should be the diagnosis given.

Fourthly, irritability as a dimension phenotype cutting across diagnoses. This concept is in agreement with the Research Domain Criteria of the National Institutes of Mental Health (NIMH), which suggests that psychopathological mechanisms and new treatment targets should be studied across diagnostic boundaries.⁴⁰ Furthermore, this perspective is consistent with the presence of chronic irritability and temper outbursts in a wide range of disorders, such as ADHD, ODD, and ASD.^{41,42} Indeed, Wakschlag et al. found that around 80% of preschool-aged children have temper loss, but only 8% have it daily.⁴³ Using Item Response Theory (IRT), the authors psychometrically validated Temper loss as a dimensional continuum ranging from normative misbehaviors to problem indicators. Thus, quality as well as frequency would contribute to a severity continuum. Indicators of concern include daily tantrums, lasting more than 5 minutes, physical aggression during the tantrum, the occurrence of a tantrum with nonparental adults, and the presence of tantrums without a trigger. Although these results were in preschoolers, thus too young for either the SMD or DMDD diagnoses, they provide support for a dimensional conceptualization.

Regardless of the classification applied, emotional dysregulation has been described as a common component of many developmental psychopathologies and a strong predictor of both disruptive and mood syndromes.⁴⁴ Although empirical evidence supports emo-

tional dysregulation as a continuum and a critical domain of research, clinical decisions remain dependent upon diagnostic categories. Driven by the concern regarding BD misdiagnosis and focused on clinicians' use, the DSM-5 deliberations point towards the adoption of DMDD. One can conclude at this time that not enough scientific data about these children are available to create a new diagnosis. However, we should agree on the importance of this problem and the need to expand the efforts to understand the complex construct of irritability.⁴⁵

In short, clinical assessment of a child presenting with irritability and temper outbursts should always start with active investigation of episodicity. Is it possible to determine when the symptoms began? Have there been significant changes relative to the child's usual baseline behavior? Did the changes occur in response to life events? Have associated symptoms occurred along with irritability? Is it possible to distinguish a clear episode of irritable mood and its associated symptoms? In the case of episodicity, proper assessment for BD should be carried on. On the contrary, if irritability is considered chronic, clinical investigation should turn towards emotional dysregulation-based diagnoses (Figure 1). DMDD phenotype should be considered if the child is described as always irritable and angry, it is difficult to determine when symptoms began (probably early in life), and temper outbursts occur frequently. It is important to

evaluate triggering events, duration and intensity of outbursts as well as settings where they usually occur (home, with family, and peers). Children with the DMDD phenotype present irritable or angry mood between outbursts, characterized as sensitive to day-to-day frustration and ordinary changes. In almost all cases, these children will present with another diagnosis, ODD being by far the most common (however, as specified above, when the comorbidity between ODD and DMDD occur, the latter should be given preference). Besides, ADHD and anxiety disorders also commonly co-occur. Of note, family history of psychopathology should be actively assessed.

Research on measurement of irritability has been limited. The Affective Reactivity Index (ARI), a scale that contains six symptom items and one impairment item about irritability, has been created to address this gap. The scale focuses on three aspects of irritability over the last 6 months: threshold for an angry reaction, frequency of anger feelings/behaviors, and duration of such feelings/behaviors. The ARI has excellent internal consistency and external validation and can be used at both research and clinical settings.⁴⁶

Therapeutic strategies for chronic irritability

Taken together, evidence of functional impairment, early onset, high morbidity, and wide spread comorbidity make

Figure 1 Assessment of irritability in children and adolescents

emotional dysregulation a critical target for intervention. Although little research has focused on the treatment of SMD/DMDD, parent training and cognitive behavioral therapy has shown promising results. Scott et al. evaluated whether children presenting the irritable dimension of ODD would be more sensitive to the positive effects of a parenting program than those without such a profile.⁴⁷ One hundred and twelve children, between 4-6 years, were randomized to the intervention (n=61) or control group (n=51). Parental intervention covered promotion of desirable child behavior through play, praise, rewards, handling misbehavior, applying consequences, and time out. Post hoc analyses indicated that treatment effect was moderated by emotional dysregulation. Although too young for meeting diagnostic criteria for either SMD or DMDD, preschool children with emotional dysregulation were more sensitive to changes in parenting and showed significantly stronger treatment effect than those without the phenotype.

Along these lines, Waxmonsky et al. proposed a group-based psychosocial treatment integrating evidence-based techniques of behavioral modification, anger management, and CBT programs to target oppositional behaviors and mood symptoms for children with ADHD plus SMD (mean age: 8.7 ± 2 years).⁴⁸ The 9-week intervention included parent sessions paralleled with child sessions and promoted joint application of learned skills for the whole family. Treatment had a large effect on the CDRS (Cohen's d 1.17), YMRS (Cohen's d 0.81), and improved Child Global Assessment Scale (CGAS: pretreatment 47.86 ± 7.5 ; posttreatment 66.43 ± 10.7). These findings provide preliminary evidence for behavioral cognitive interventions. Moreover, the inclusion of the parents in the intervention seems crucial for treatment effectiveness.

Addressing pharmacological options for the treatment of emotional dysregulation, the only placebo-controlled trial in children with SMD found no benefit of lithium over placebo.⁴⁹ An open label trial using low doses (mean 1.2 ± 0.5 mg) of risperidone in children and adolescents with SMD showed significant reductions in irritability scores (Aberrant Behavior Checklist-Irritability at baseline 25.89, standard error [SE] 2.7, and at week 8 11.28, SE 3.06, $p < 0.001$).⁵⁰ Risperidone was also effective in reducing duration of rage outbursts in inpatient settings (baseline 44 ± 20 min, last dose 25 ± 12 min).⁵¹ Indeed, risperidone is FDA approved for the treatment of irritability in patients with autism spectrum disorders, although irritability in autism may not be the same as the one found in typically developing children. However, such findings should be seen with caution, especially because of the potential damaging side effects of antipsychotics in youth.

In addition, some studies show support for the use of stimulants in patients exhibiting ADHD plus SMD symptoms. A study examining the effect of stimulants in children with ADHD and SMD found the association to be safe and to reduce externalizing symptoms.⁵² Studies examining emotional lability in ADHD provide additional support for the use of stimulants in this population.⁵³ A randomized controlled trial, conducted by the NIMH mood disorders team using citalopram plus methylphenidate in children

with SMD, is under way. The rationale for use selective serotonin reuptake inhibitors (SSRIs) in children with SMD is the clear link between this phenotype and depressive disorders. The concern of using antidepressants in these children is no longer valid, since the boundaries with BD are well established. There is, however, a clear need for further studies on treatment strategies in children presenting with chronic irritability and temper outbursts. Furthermore, as comorbidity seems to be the rule, trials addressing therapeutic strategies according to comorbid disorders are much needed.

Conclusion

Irritability has been surrounded by controversy in child and adolescent psychiatry. First, the debate was driven by the boundaries between chronic irritability and bipolar diagnosis. Once the boundaries with BD were clarified, the debate turned to the proposal of a new diagnosis category, whose main symptom is emotional dysregulation. Although evidence suggests a dimensional distribution across the pediatric population, the DSM-5 indicates the adoption of DMDD as a new category entity. The associations of emotional dysregulation phenotypes are wide and include both internalizing and externalizing disorders, but are mainly linked to depressive disorders. Finally, treatment evidence includes cognitive behavioral therapy, especially parental intervention, but there is a pressing need for research on adjunctive pharmacological treatment.

Acknowledgements

This study was supported by a PhD scholarship received by the first author from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Brazil.

Disclosure

Fernanda Valle Krieger has served as a speaker to Shire Pharmaceuticals. Guilherme V. Polanczyk has served as a speaker and/or consultant to Eli-Lilly, Novartis, Janssen-Cilag, and Shire Pharmaceuticals; has developed educational material to Janssen-Cilag; receives authorship royalties from Manole Editors; and has received unrestricted research support from Novartis. The other authors report no conflicts of interest.

References

- 1 Leibenluft E. Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. *Am J Psychiatry*. 2011;168:129-42.
- 2 Sroufe LA, Rutter M. The domain of developmental psychopathology. *Child Dev*. 1984;55:17-29.
- 3 Kim-Cohen J, Caspi A, Moffitt TE, Harrington H, Milne BJ, Poulton R. Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. *Arch Gen Psychiatry*. 2003;60:709-17.
- 4 Copeland WE, Shanahan L, Costello EJ, Angold A. Childhood and adolescent psychiatric disorders as predictors of young adult disorders. *Arch Gen Psychiatry*. 2009;66:764-72.

- 5 Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62:593-602.
- 6 Blader JC, Carlson GA. Increased rates of bipolar disorder diagnoses among U.S. child, adolescent, and adult inpatients, 1996-2004. *Biol Psychiatry*. 2007;62:107-14.
- 7 Moreno C, Laje G, Blanco C, Jiang H, Schmidt AB, Olfson M. National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. *Arch Gen Psychiatry*. 2007;64:1032-9.
- 8 American Psychiatric Association. Diagnostic and statistical manual of mental disorders - DSM-IV-TR®. 4th ed. Arlington: American Psychiatric Publishing; 1994.
- 9 Leibenluft E, Charney DS, Pine DS. Researching the pathophysiology of pediatric bipolar disorder. *Biol Psychiatry*. 2003;53:1009-20.
- 10 Wozniak J, Biederman J, Kiely K, Ablon JS, Faraone SV, Mundy E, et al. Mania-like symptoms suggestive of childhood-onset bipolar disorder in clinically referred children. *J Am Acad Child Adolesc Psychiatry*. 1995;34:867-76.
- 11 Biederman J, Klein RG, Pine DS, Klein DF. Resolved: mania is mistaken for ADHD in prepubertal children. *J Am Acad Child Adolesc Psychiatry*. 1998;37:1091-6; discussion 1096-9.
- 12 Biederman J, Faraone SV, Wozniak J, Mick E, Kwon A, Aleardi M. Further evidence of unique developmental phenotypic correlates of pediatric bipolar disorder: findings from a large sample of clinically referred preadolescent children assessed over the last 7 years. *J Affect Disord*. 2004;82:S45-58.
- 13 Carlson GA, Meyer SE. Phenomenology and diagnosis of bipolar disorder in children, adolescents, and adults: complexities and developmental issues. *Dev Psychopathol*. 2006;18:939-69.
- 14 Leibenluft E, Blair RJ, Charney DS, Pine DS. Irritability in pediatric mania and other childhood psychopathology. *Ann N Y Acad Sci*. 2003;1008:201-18.
- 15 Leibenluft E, Cohen P, Gorrindo T, Brook JS, Pine DS. Chronic versus episodic irritability in youth: a community-based, longitudinal study of clinical and diagnostic associations. *J Child Adolesc Psychopharmacol*. 2006;16:456-66.
- 16 Leibenluft E, Charney DS, Towbin KE, Bhangoo RK, Pine DS. Defining clinical phenotypes of juvenile mania. *Am J Psychiatry*. 2003;160:430-7.
- 17 Brotman MA, Kassem L, Reising MM, Guyer AE, Dickstein DP, Rich BA, et al. Parental diagnoses in youth with narrow phenotype bipolar disorder or severe mood dysregulation. *Am J Psychiatry*. 2007;164:1238-41.
- 18 Stringaris A, Cohen P, Pine DS, Leibenluft E. Adult outcomes of youth irritability: a 20-year prospective community-based study. *Am J Psychiatry*. 2009;166:1048-54.
- 19 Stringaris A, Baroni A, Haimm C, Brotman M, Lowe CH, Myers F, et al. Pediatric bipolar disorder versus severe mood dysregulation: risk for manic episodes on follow-up. *J Am Acad Child Adolesc Psychiatry*. 2010;49:397-405.
- 20 Adleman NE, Fromm SJ, Razdan V, Kayser R, Dickstein DP, Brotman MA, et al. Cross-sectional and longitudinal abnormalities in brain structure in children with severe mood dysregulation or bipolar disorder. *J Child Psychol Psychiatry*. 2012;53:1149-56.
- 21 Rich BA, Schmajuk M, Perez-Edgar KE, Fox NA, Pine DS, Leibenluft E. Different psychophysiological and behavioral responses elicited by frustration in pediatric bipolar disorder and severe mood dysregulation. *Am J Psychiatry*. 2007;164:309-17.
- 22 Rau G, Blair KS, Berghorst L, Knopf L, Skup M, Luckenbaugh DA, et al. Processing of differentially valued rewards and punishments in youths with bipolar disorder or severe mood dysregulation. *J Child Adolesc Psychopharmacol*. 2008;18:185-96.
- 23 Duffy A. The nature of the association between childhood ADHD and the development of bipolar disorder: a review of prospective high-risk studies. *Am J Psychiatry*. 2012;169:1247-55.
- 24 Birmaher B, Axelson D, Goldstein B, Strober M, Gill MK, Hunt J, et al. Four-year longitudinal course of children and adolescents with bipolar spectrum disorders: the Course and Outcome of Bipolar Youth (COBY) study. *Am J Psychiatry*. 2009;166:795-804.
- 25 McLaughlin KA, Hatzenbuehler ML, Mennin DS, Nolen-Hoeksema S. Emotion dysregulation and adolescent psychopathology: a prospective study. *Behav Res Ther*. 2011;49:544-54.
- 26 Deveney CM, Connolly ME, Jenkins SE, Kim P, Fromm SJ, Pine DS, et al. Neural recruitment during failed motor inhibition differentiates youths with bipolar disorder and severe mood dysregulation. *Biol Psychol*. 2012;89:148-55.
- 27 Thomas LA, Brotman MA, Muhrer EJ, Rosen BH, Bones BL, Reynolds RC, et al. Parametric modulation of neural activity by emotion in youth with bipolar disorder, youth with severe mood dysregulation, and healthy volunteers. *Arch Gen Psychiatry*. 2012;69:1257-66.
- 28 Brotman MA, Schmajuk M, Rich BA, Dickstein DP, Guyer AE, Costello EJ, et al. Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. *Biol Psychiatry*. 2006;60:991-7.
- 29 American Psychiatric Association. DSM-5 Development [Internet]. 2012 [cited 2013 Jun 17]. <http://www.dsm5.org/>
- 30 Copeland WE, Angold A, Costello EJ, Egger H. Prevalence, comorbidity, and correlates of DSM-5 proposed disruptive mood dysregulation disorder. *Am J Psychiatry*. 2013;170:173-9.
- 31 Axelson D, Findling RL, Fristad MA, Kowatch RA, Youngstrom EA, Horwitz SM, et al. Examining the proposed disruptive mood dysregulation disorder diagnosis in children in the Longitudinal Assessment of Manic Symptoms study. *J Clin Psychiatry*. 2012;73:1342-50.
- 32 Stringaris A, Goodman R. Three dimensions of oppositionality in youth. *J Child Psychol Psychiatry*. 2009;50:216-23.
- 33 Stringaris A, Goodman R. Longitudinal outcome of youth oppositionality: irritable, headstrong, and hurtful behaviors have distinctive predictions. *J Am Acad Child Adolesc Psychiatry*. 2009;48:404-12.
- 34 Stringaris A, Maughan B, Goodman R. What's in a disruptive disorder? Temperamental antecedents of oppositional defiant disorder: findings from the Avon longitudinal study. *J Am Acad Child Adolesc Psychiatry*. 2010;49:474-83.
- 35 Rowe R, Costello EJ, Angold A, Copeland WE, Maughan B. Developmental pathways in oppositional defiant disorder and conduct disorder. *J Abnorm Psychol*. 2010;119:726-38.
- 36 Ezpeleta L, Granero R, de la Osa N, Penelo E, Domènech JM. Dimensions of oppositional defiant disorder in 3-year-old preschoolers. *J Child Psychol Psychiatry*. 2012;53:1128-38.
- 37 Drabick DA, Gadow KD. Deconstructing oppositional defiant disorder: clinic-based evidence for an anger/irritability phenotype. *J Am Acad Child Adolesc Psychiatry*. 2012;51:384-93.
- 38 Stringaris A, Zavos H, Leibenluft E, Maughan B, Eley TC. Adolescent irritability: phenotypic associations and genetic links with depressed mood. *Am J Psychiatry*. 2012;169:47-54.
- 39 Krieger FV, Polanczyk VG, Robert G, Rohde LA, Graeff-Martins AS, Salum G, et al. Dimensions of oppositionality in a Brazilian community sample: testing the DSM-5 proposal and etiological links. *J Am Acad Child Adolesc Psychiatry*. 2013;52:389-400.
- 40 Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry*. 2010;167:748-51.
- 41 Skirrow C, McLoughlin G, Kuntsi J, Asherson P. Behavioral, neurocognitive and treatment overlap between attention-deficit/hyperactivity disorder and mood instability. *Expert Rev Neurother*. 2009;9:489-503.
- 42 Simonoff E, Jones CR, Pickles A, Happé F, Baird G, Charman T. Severe mood problems in adolescents with autism spectrum disorder. *J Child Psychol Psychiatry*. 2012;53:1157-66.
- 43 Wakschlag LS, Henry DB, Tolan PH, Carter AS, Burns JL, Briggs-Gowan MJ. Putting theory to the test: modeling a multidimensional, developmentally-based approach to preschool disruptive behavior. *J Am Acad Child Adolesc Psychiatry*. 2012;51:593-604.
- 44 Stringaris A, Goodman R. Mood lability and psychopathology in youth. *Psychol Med*. 2009;39:1237-45.
- 45 Axelson D. Taking disruptive mood dysregulation disorder out for a test drive. *Am J Psychiatry*. 2013;170:136-9.
- 46 Stringaris A, Goodman R, Ferdinando S, Razdan V, Muhrer E, Leibenluft E, et al. The Affective Reactivity Index: a concise irritability scale for clinical and research settings. *J Child Psychol Psychiatry*. 2012;53:1109-17.
- 47 Scott S, O'Connor TG. An experimental test of differential susceptibility to parenting among emotionally-dysregulated children in a randomized controlled trial for oppositional behavior. *J Child Psychol Psychiatry*. 2012;53:1184-93.

- 48 Waxmonsky JG, Wymbs FA, Pariseau ME, Belin PJ, Waschbusch DA, Babocsai L, et al. A novel group therapy for children with ADHD and severe mood dysregulation. *J Atten Disord*. 2012 Feb 28. [Epub ahead of print]
- 49 Dickstein DP, Towbin KE, Van Der Veen JW, Rich BA, Brotman MA, Knopf L, et al. Randomized double-blind placebo-controlled trial of lithium in youths with severe mood dysregulation. *J Child Adolesc Psychopharmacol*. 2009;19:61-73.
- 50 Krieger FV, Pheula GF, Coelho R, Zeni T, Tramontina S, Zeni CP, et al. An open-label trial of risperidone in children and adolescents with severe mood dysregulation. *J Child Adolesc Psychopharmacol*. 2011;21:237-43.
- 51 Carlson GA, Potegal M, Margulies D, Basile J, Gutkovich Z. Liquid risperidone in the treatment of rages in psychiatrically hospitalized children with possible bipolar disorder. *Bipolar Disord*. 2010;12:205-12.
- 52 Waxmonsky J, Pelham WE, Gnagy E, Cummings MR, O'Connor B, Majumdar A, et al. The efficacy and tolerability of methylphenidate and behavior modification in children with attention-deficit/hyperactivity disorder and severe mood dysregulation. *J Child Adolesc Psychopharmacol*. 2008;18:573-88.
- 53 Rosler M, Retz W, Fischer R, Ose C, Alm B, Deckert J, et al. Twenty-four-week treatment with extended release methylphenidate improves emotional symptoms in adult ADHD. *World J Biol Psychiatry*. 2010;11:709-18.

5.1.1 Discussão Artigo 1

O artigo intitulado “Irritability in children and adolescents: past concepts, current debates, and future opportunities” é um trabalho de revisão publicado na Revista Brasileira de Psiquiatria em 2013 que teve como objetivo apresentar a controvérsia acerca do papel da irritabilidade na classificação diagnóstica dos transtornos mentais em crianças e adolescentes.

A primeira seção do artigo introduz o debate iniciado a partir da observação do aumento exponencial no diagnóstico de Transtorno de Humor Bipolar em crianças e adolescentes. A irritabilidade foi apontada como o fator causal predominante para o aumento na prevalência de TB na população pediátrica a partir do final da década de 90. De fato, crianças que apresentavam crises raiva frequentes, baixa tolerância à frustração e humor irritado vinham sistematicamente recebendo o diagnóstico de TB. Estudos subsequentes demonstraram que a apresentação clínica da irritabilidade (episódica vs. crônica) determinava diferentes trajetórias psicopatológicas. A irritabilidade de curso episódico geralmente associada a grandiosidade, diminuição da necessidade do sono, sintomas psicóticos e caracterizada por períodos intercalados de eutímia possui maior correlação com TB. Por outro lado, a irritabilidade de curso crônico, caracterizada por baixa tolerância à frustração e frequentes crises de raiva, sem períodos de melhora ou flutuação é preditora de transtornos de ansiedade e depressivos. Logo, indivíduos apresentando irritabilidade crônica vinham recebendo desnecessariamente o diagnóstico de TB.

Diante do esclarecimento entre irritabilidade de curso episódico e crônico, se evidenciou a necessidade de uma “categoria diagnóstica” para aqueles com irritabilidade crônica. Inúmeras categorias foram propostas e na segunda parte desta revisão exemplificamos 4 formas de classificar estes indivíduos. O primeiro deles foi chamado de “Severe Mood Dysregulation (SMD)”, categoria que teve por objetivo principal estabelecer a diferenciação clínica com TB. O SMD deu origem ao “Disruptive Mood Dysregulation Disorder (DMDD)” categoria incluída na classificação diagnóstica no DSM-5, cujo sintoma principal é irritabilidade crônica, com frequentes crises de raiva. Entretanto, uma terceira forma de classificar estas crianças é a dimensão

irritável do Transtorno de Oposição e Desafio (TOD), cujos sintomas se assemelham ao SMD e DMDD, inclusive com as mesmas associações e prognóstico. Uma quarta forma de entender a irritabilidade crônica foi recentemente proposta pelo Research Domain Criteria (RDoC) e sugere a irritabilidade como uma dimensão que subjaz inúmeros transtornos e não parece ser específica a nenhum deles.

Na parte final do artigo propomos um fluxograma de avaliação da irritabilidade em crianças e adolescentes. O fenótipo da irritabilidade em crianças e adolescentes segue tópico de discussão e controvérsia tanto em ambientes clínicos como de pesquisa. Entretanto, uma avaliação detalhada permite identificar e conduzir a estratégias mais adequadas. A intervenção parental é fator predominante e crucial para o sucesso do tratamento.

5.2 Artigo 2

**“Dimensions of oppositionality in a Brazilian community sample:
Testing the DSM-5 proposal and etiological links”**

Dimensions of Oppositionality in a Brazilian Community Sample: Testing the *DSM-5* Proposal and Etiological Links

Fernanda Valle Krieger, M.D., Guilherme Vanoni Polanczyk, M.D., Ph.D.,
Robert Goodman, Ph.D., F.R.C.Psych., Luis Augusto Rohde, M.D., Ph.D.,
Ana Soledade Graeff-Martins, M.D., Ph.D., Giovanni Salum, M.D., Ph.D., Ary Gadelha, M.D.,
Pedro Pan, M.D., Daniel Stahl, Ph.D., Argyris Stringaris, M.D., Ph.D., M.R.C.Psych.

Objective: Investigating dimensions of oppositional symptoms may help to explain heterogeneity of etiology and outcomes for mental disorders across development and provide further empirical justification for the *DSM-5*–proposed modifications of oppositional defiant disorder (ODD). However, dimensions of oppositionality have not previously been tested in samples outside Europe or the United States. In this study, we used a large Brazilian community sample to compare the fit of different models for dimensions of oppositional symptoms; to examine the association of psychiatric diagnoses and symptoms with dimensions of oppositionality; and to examine the associations between dimensions of oppositionality and parental history of mental disorders. **Method:** A Brazilian community sample of 2,512 children 6 through 12 years old were investigated in this study. Confirmatory factorial analyses were performed to compare the fit of alternative models, followed by linear and logistic regression analyses of associations with psychiatric diagnosis and parental history of psychopathology. **Results:** A three-factor model with irritable, headstrong, and hurtful dimensions fitted best. The irritable dimension showed a strong association with emotional disorders in the child ($p < .001$) and history of depression ($p < .01$) and suicidality ($p < .05$) in the mother. The headstrong dimension was uniquely associated with attention-deficit/hyperactivity disorder (ADHD) in the child ($p < .001$) and with maternal history of ADHD symptoms ($p < .05$). The hurtful dimension was specifically associated with conduct disorder ($p < .05$). **Conclusions:** Our findings from a large community sample of Brazilian children support a distinction between dimensions of oppositionality consistent with current *DSM-5* recommendations and provide further evidence for etiological distinctions between these dimensions. *J. Am. Acad. Child Adolesc. Psychiatry*; 2013;52(4):389–400. **Key Words:** oppositionality, dimensions, irritability, depression.

The identification of distinct dimensions of oppositional symptoms may help to explain heterogeneity of etiology and outcomes of mental disorders across development.¹ The *DSM-5* process has recently suggested a distinction among irritable, headstrong, and hurtful dimensions in its update on oppositional defiant disorder (ODD).² However, the evidence for this distinction derives exclusively from European and North American samples, and it is currently

unclear whether it applies to other populations. Moreover, there are many outstanding questions about etiological distinctions between dimensions of oppositionality. To address this gap, the present study examines dimensions of oppositionality with regard to their factorial structure, psychiatric correlates, and distinct familial risk factors within a large community-based Brazilian sample of children.

Oppositional defiant disorder (ODD)—a persistent pattern of negativistic, hostile, and defiant behavior that is classified as a disruptive behavior disorder³—is one of the most common childhood psychiatric disorders.⁴ ODD is strongly associated with other disruptive behavior disorders, such as

Clinical guidance is available at the end of this article.

Supplemental material cited in this article is available online.

attention-deficit/hyperactivity disorder (ADHD) and conduct disorder (CD),⁵ but also with internalizing disorders, such as depression and anxiety.⁶ ODD often progresses to CD,^{5,7,8} but is also one of the most robust predictors of adolescent and young adult depression.⁹ Indeed, ODD is part of the developmental history of a wide range of disorders in youth and adults.¹⁰

Considering the heterogeneity within the ODD construct, Stringaris and Goodman¹¹ provided cross-sectional and longitudinal evidence for the existence of three distinct dimensions or constructs within the ODD diagnosis: irritable, headstrong, and hurtful. The irritable dimension includes symptoms of temper outbursts, touchiness, and anger, and shows specific associations with emotional disorders. The headstrong dimension includes symptoms of arguing with grown ups, annoying others on purpose, refusing to follow rules, and blaming others for his or her own mistakes, and shows specific association with ADHD. The hurtful dimension includes symptoms of spitefulness and vindictiveness. Although all three dimensions showed cross-sectional associations with conduct problems, the hurtful dimension was differentially associated with aggressive conduct problems and callous-unemotional (CU) traits in a 3-year follow-up study.¹²

Since these findings, several groups have examined the fractionation of oppositionality into dimensions. Aebi *et al.*¹³ findings support the three-factor model initially identified by Stringaris and Goodman. Burke *et al.*¹⁴ found a three-factor solution with different aggregation of symptoms: a negative affective factor, including symptoms such as anger, touchiness, and spitefulness; an oppositional behavior factor, including symptoms such as temper outbursts, arguing, and defying; and an antagonistic behavior factor, including symptoms such as annoying and blaming others. Rowe *et al.* identified a two-factor solution, distinguishing between irritable and headstrong symptoms, an approach similar to the approach used by Stringaris *et al.* in a twin sample.^{15,16} In both studies, the authors were working with samples in which only one hurtful item had been measured, and included this in a broader headstrong dimension. Nevertheless, their findings confirmed that the irritable dimension was differentially strongly associated with anxiety/depression and the other dimension was strongly correlated to conduct disorder. Recently,

Ezpeleta *et al.* and Wakschlag *et al.* extended findings on oppositional dimensions to preschool samples.^{17,18}

Based on this evidence, the DSM-5 Task Force suggested a modification of the diagnosis of ODD subdividing its current eight items into three subgroups: angry/irritable mood, argumentative/defiant behavior, and vindictiveness.² However, further evidence is required to examine the proposed separation. First, the question about the best model structure, that is, of the best way to carve up oppositionality, is still open. There are a number of competing models of dimensions in oppositionality, and there is no work to compare which model gives the best account of the data. Second, although the DSM is used internationally for research and clinical purposes, so far all studies on oppositionality and its distinct associations with psychopathology derive exclusively from European or North American populations. Neither the structure of oppositional symptoms nor its associations with other psychopathology have been tested in samples from other parts of the world. However, it is important to study samples from other cultures to determine whether the distinction between dimensions of oppositionality is a universal or a culturally restricted phenomenon and whether the proposed nosological distinctions are applicable worldwide. Third, there is a need to understand better etiological distinctions. The evidence on specific cross-sectional and longitudinal associations suggests distinct etiological underpinnings. Indeed, in a twin-based approach, Stringaris *et al.* showed evidence of genetic overlap between irritability and depression on the one hand, and between headstrong/hurtful and delinquency on the other.¹⁵ However, there is little further research on possible etiological distinctions. Family history is an important factor in the etiology of psychiatric disorders and disruptive behaviors are known to be highly heritable.¹⁹ There are associations between maternal depression and psychiatric disorders in the offspring and children of depressed mothers are at greater risk for both internalizing and externalizing disorders.^{20–22} This raises the question as to whether the dimensions could be distinguished on the basis of family history.

To address these gaps in knowledge, we used a large community sample of Brazilian children who were well characterized in terms of psychiatric diagnosis and family history, to address key

issues in regard to the dimensions of oppositionality. Our aims were as follows: first, to compare the fit of different models that have been previously reported in the literature for distinguishing between dimensions of oppositional symptoms. For this purpose, we compared a one-factor structure (all ODD items forming one dimension, as originally proposed by the *DSM-IV*) versus a two-factor structure (irritable and headstrong/hurtful) versus the three-factor structure proposed by Stringaris and also by the *DSM-5* Working Group (irritable, headstrong, and hurtful) versus the three-factor structure proposed by Burke *et al.* (negative affect, oppositional behavior, and antagonistic behavior). Our second goal was to examine the pattern of associations between the dimensions of the best-fitting model and psychiatric diagnosis and symptoms. Our third goal was to examine the associations between dimensions of oppositionality and parental history of mental disorders. Our hypotheses were: The best fitting model would be the three-factor model with irritable, headstrong, and hurtful dimensions; second, associations would be detected between the irritable/negative affective dimension and emotional disorders, between the headstrong/oppositional behavioral dimension and ADHD, and between the hurtful dimension and conduct disorder; and third, associations would be detected between the irritable/negative affective dimensions and a family history of depression; between headstrong/oppositional behavior and a parental history of ADHD symptoms; and between the hurtful dimension and a parental history of antisociality and incarceration.

METHOD

Sample

This report is part of a large, community, school-based study that combines standardized evaluation from a psychiatric and cognitive neuroscience perspective, as well as genetics and neuroimaging, to inform preventive strategies in developmental psychiatry. It was performed in multiple steps involving several evaluation teams and research protocols as previously described.²³ These steps, described here briefly, included screening, psychiatric assessments, and cognitive evaluation. Our study population in the screening phase was composed of students from public schools located close to the research centers in Porto Alegre and São Paulo, Brazil. A total of 57 schools from the two cities (22 schools in Porto Alegre and 35 schools

in São Paulo) participated in the screening and enrolment procedures. Eligible subjects were those with the following characteristics: registered for school by a biological parent capable of providing consent and information about the child's behavior; 6 to 12 years of age; and having remained in the same school during the year for logistic reasons. For screening, 9,937 informant interviews based on the Family History Survey (FHS)²⁴ were conducted (involving the child's biological mother in 88% of the families). From this pool, we selected two subgroups: a random and a high-risk stratum. For subjects in the random-selection stratum, a simple randomization procedure from school directories was used, without replacement of unavailable subjects. Selection for the high-risk stratum involved a risk-prioritization procedure, focused on individuals with a family history of a disorder and/or ongoing symptoms in one of the five targeted domains (attention-deficit/hyperactivity disorder [ADHD], anxiety, obsessive-compulsive disorder [OCD], psychosis, and learning disorders), as detected during screening. Subjects in this second high-risk stratum were oversampled and replaced by the next subject listed in the sampling frame of higher risk if not available. From 1,315 children selected in the first random stratum, 958 (73%) completed the household evaluation. There were no differences in gender, number of siblings, or presence of depressive symptoms in mothers between those who did and those who did not participate in the survey; those who participated in the study were younger (entered: 8.6 years; did not enter: 9.1 years; $p < .001$). From the 2,050 children selected for the high-risk stratum, 1,554 (76%) participated in the study. There were no differences in age, gender, number of siblings, or depressive symptoms in mothers between those who did and those who did not participate. The total sample was a combination of the random and the high-risk samples and included 2,512 subjects. Written consent was obtained from all parents of participants, and verbal assent was obtained from all children. When appropriate, written assent was also obtained. The study was approved by the ethics committee of the University of São Paulo (IORG0004884, project IRB registration number: 1132/08).

Measures

Strengths and Difficulties Questionnaire (SDQ). This is a 25-item questionnaire with robust psychometric properties. It comprises five factors, each one with five items: emotional problems, hyperactivity, conduct problems, peer problems, and prosociality.²⁵ The reliability and validity of SDQ make it a good measure of the adjustment of psychopathology of children and adolescents.²⁶ Although there are also youth and teacher SDQ versions, only the parental version was used on the study for logistic reasons. Here, we tested the SDQ scores of 2,512 children as dependent variables for

association with the oppositional dimensions as predictors.

Development and Well-Being Assessment (DAWBA). This is a structured interview administered by lay interviewers who also recorded the verbatim accounts of any reported problems.^{27,28} The questions are closely related to *DSM-IV* and *ICD-10* diagnostic criteria and focus on current problems. The DAWBA makes use of skip rules that allow interviewers to omit many of the detailed questions in a section when the preliminary answer indicates a very low probability of disorder in that domain. In the case of oppositional defiant disorder (ODD), the detailed questions are skipped if both of the following conditions are met: the behavior of the child is not reported to be more troublesome than that of other children at the same age, and the conduct problems score on the SDQ is in the normal range. In the present study, 50.7% (1,274) of the sample were assessed for ODD. When the two "skip" conditions are not met, the DAWBA asks nine questions on ODD, one question on each of the 7 first *DSM-IV* items and the 2 separate questions for the "spiteful and vindictive" item. The response categories were "no more than others" (0), "a little more than others" (1), and "a lot more than others" (2). To create dimensions of oppositionality, we grouped the DAWBA's ODD items in the four following models: first, a one-factor model, in which all nine items were loaded; second, a two-factor model: irritable and headstrong/hurtful model, using three items for irritable ("had temper outbursts?" "been touchy and easily annoyed?" "been angry and resentful?") and six items for headstrong/hurtful ("argued with grown-ups?" "taken no notice of rules, or refused to do as s/he is told?" "seemed to do things to annoy other people on purpose?" "blamed others for his/her own mistakes?" "been spiteful?" "been vindictive?"); third, a three-factor model following Stringaris *et al.*: an irritable, headstrong, and hurtful model, preserving the irritable with three items as above ("had temper outbursts?" "been touchy and easily annoyed?" "been angry and resentful?"), headstrong with four items ("argued with grown-ups?" "taken no notice of rules, or refused to do as s/he is told?" "seemed to do things to annoy other people on purpose?" "blamed others for his/her own mistakes?"), and two items for hurtful ("been spiteful?" "been vindictive?"); and fourth, a three-factor model following Burke *et al.*: negative affective, oppositional behavior and antagonistic behavior model, using four items for negative affective dimension ("been angry and resentful?" "been spiteful?" "been vindictive?" "been touchy and easily annoyed?"), three items for oppositional behavior ("had temper outbursts?" "argued with grown-ups?" "taken no notice of rules, or refused to do as s/he is told?"), and two items for antagonist behavior ("seemed to do things to annoy other people on purpose?" "blamed others for his/her own mistakes?") (see Figure S1, available online).

Mini-International Neuropsychiatric Interview (M.I.N.I.). This is a short, structured diagnostic interview, for *DSM-IV* and *ICD-10* psychiatric disorders in adults. The M.I.N.I. has acceptably high validation and reliability scores.²⁹ In the present study, the M.I.N.I. was administered during the household evaluation to biological mothers in 91.5% of cases. For the analyses presented in this article, we considered a family history of depression, suicidality, childhood symptoms of ADHD, and drinking as dependent variables, examining how far they were predicted by the oppositional dimensions.

Family History Screen (FHS). This is a screening instrument that was used for parental history of incarceration and childhood conduct symptoms as dependent variables for association with the oppositional dimensions as predictors.

Participants With Data on Dimensions of Oppositionality

There were 2,512 children for whom there were available clinical and demographic data (see above). The characteristics of the oppositional dimensions subsample ("dimensions subsample," i.e., those who responded affirmatively to the DAWBA's ODD skip question, $n = 1,274$) and the non-dimensions subsample ($n = 1,238$) are summarized on Table 1. There were no differences in age, gender, or maternal education between the two groups. The oppositional dimensions subsample was more likely to come from low and very low socioeconomic backgrounds (dimensions: 16.5%; non-dimensions: 12.5%; $p = .004$) and presented significantly more "any psychiatric diagnosis" (dimensions: 40.2%; non-dimensions: 11.2%; $p < .001$), ODD (dimensions: 10.2%; non-dimensions: 0; $p < .001$), CD (dimensions: 3.1%; non-dimensions: 0; $p < .001$), ADHD (dimensions: 19.3%; non-dimensions: 2.2%; $p < .001$) and emotional disorders (dimensions, 18.6%; non-dimensions, 7.8%; $p < .001$). The differences listed above were expected, because the oppositional dimensions subsample was composed by those individuals who passed through the DAWBA's skip rule for ODD, thus increasing their likelihood of having a disruptive and/or an emotional diagnosis.

Statistical Analysis

Confirmatory factorial analyses (CFA) were used to compare the goodness-of-fit between the following ODD models separately: one factor; two factors (irritable, headstrong/hurtful), three factors (irritable, headstrong, and hurtful; negative affective, oppositional behavioral, and antagonist behavior). Goodness-of-fit was assessed in all models using Tucker Lewis Index (TLI), Comparative Fit Index (CFI), root mean square error of approximation (RMSEA). For CFI and TLI, values greater than 0.95 are preferred, and values near

TABLE 1 Sample Characteristics

	Age, Y, Mean (SD)	Male n (%)	Socioeconomic Status n (%)			Maternal Education: Completed High School n (%)	Any Diagnosis n (%)	ODD n (%)	CD n (%)	ADHD n (%)	Emotional Disorders n (%)
			Low– Very Low	Medium	High						
Dimensions	1274 9.67 (1.9)	694 (54.4)	211 (16.5)	940 (73.7)	123 (9.6)	503 (39.9)	513 (40.2)	131 (10.2)	40 (3.1)	246 (19.3)	238 (18.6)
Non-dimensions	1238 9.73 (1.9)	641 (51.7)	155 (12.5)	927 (74.8)	515 (42.0)	515 (42.0)	139 (11.2)	0	0	28 (2.2)	97 (7.8)
	2512 NS	NS	p = .004	NS	p = .01	NS	p < .0001	p < .0001	p < .0001	p < .0001	p < .0001

Note: Top row of table represents the oppositional dimensions subsample, i.e. those who passed through the Development and Well-Being Assessment (DAWBA)'s skip rule for ODD. Bottom row represents non-dimension subsample those who did not pass the DAWBA's skip rule for ODD. ADHD = attention-deficit/hyperactivity disorder; CD = conduct disorder; NS = not significant; ODD = oppositional defiant disorder.

0.90 are considered acceptable. For RMSEA, values of 0.05 or less are preferred, and values up to 0.08 are considered acceptable.³⁰ We compared models using the Akaike Information Criteria (AIC) and the Bayesian Information Criteria (BIC), in which lower values indicate better fit.³¹ The difference between the two models was calculated as the Δ AIC and Δ BIC. These are calculated as the difference between a candidate model and the best (i.e., lowest AIC or BIC model); as an example, in the comparison between the one- and two-factor models, we calculate as follows: Δ AIC = AIC_{one factor} – AIC_{two factors}. Values of Δ AIC or Δ BIC equal to or greater than 10 indicate overwhelming support for the lower AIC and BIC models.³²

In addition, χ^2 difference tests ($\Delta\chi^2$) were conducted to compare the nested models of interest (one-factor model, two-factor [model irritable, headstrong/hurtful], and three-factor model [irritable, headstrong, and hurtful]). Those difference tests were also conducted using robust maximum likelihood and weighted least-square estimation, which showed the same pattern of results (available upon request). As the three-factor model (irritable, headstrong, and hurtful) and the three-factor model (negative affective, oppositional, and antagonistic behavior) were not nested in each other, they were compared using AIC and BIC. Analysis were performed with MPlus version 5.³³

Multivariate logistic and linear regression analyses were conducted to test the association between family history of psychopathology, comorbidities, and SDQ scores and dimensions of oppositionality. The variables corresponding to oppositional dimensions were created based on sums of scores on DAWBA's ODD items (0 = "no more than others, 1 = "a little more than others" and 2 = "a lot more than others") divided by the number of items for each dimension. Multivariate linear regression models were run for the SDQ outcomes (with the three dimensions as independent variables, controlled for age and gender), and multivariate logistic regression models were run for the disorder outcomes (with the three dimensions as independent variables, controlled for age and gender); standardized coefficients and odds ratios are reported for the linear and logistic models, respectively. To compare the size of coefficients of the dependent variables that entered the final model, we used a z test (post-estimation function *lincom*). This tests the null hypothesis that the two coefficients are equal. An alpha level of 0.05, two-tailed, was considered significant. Analysis were performed with Stata version 10.³⁴

RESULTS

Our first aim was to compare the goodness-of-fit of the four competing models for the oppositional dimensions through confirmatory factor analysis. The results of confirmatory factorial analysis for

each model are displayed in Table 2. The upper part of Table 2 presents the goodness-of-fit parameters for each model. The three-factor model (irritable, headstrong, and hurtful) fitted the data best on all parameters: values closest to 0.95 CFI and TLI; values closest to 0.05 for RMSEA; and the largest AIC and BIC. The bottom part of Table 2 displays the results for the comparisons between models. The three-factor model structured by irritable, headstrong and hurtful was superior to the one-factor (ΔAIC 583.765, ΔBIC 237.216, and χ^2 difference test 244.367, 1 df, $p < .001$) and two-factor models (ΔAIC 361.398, ΔBIC 331.099, and χ^2 difference test 345.398, 2 df, $p < 0.001$). The three-factor model comprising negative affective, oppositional, and antagonistic behavior was significantly better than the one-factor model (ΔAIC 78.565, ΔBIC 63.114, and χ^2 difference test 84.565, 3 df, $p < 0.001$), however, the three-factor model comprising negative affective, oppositional, and antagonistic behavior performed worse than the two-factor model irritable, headstrong/hurtful (ΔAIC -163.803, ΔBIC -174.102). Finally the two three-factor models were compared, and the one structured by irritable, headstrong, and hurtful best fitted the data (ΔAIC 505.2, ΔBIC 505.201).

The correlations among the three dimensions were as follows: irritable and headstrong, $r = 0.73$; irritable and hurtful, $r = 0.53$; and headstrong and hurtful, $r = 0.59$. Correlations were all highly significant ($p < .001$).

Our second aim was to adopt the best-fitting model and to examine the differential associations of each dimension with SDQ scores and psychopathology. Table 3 displays the results from linear regression within the oppositional dimensions as independent variables and SDQ scores as dependent variables. The irritable dimension showed a strong association with emotional problems ($p < .001$), and the coefficient of association for irritable was significantly higher compared to those for headstrong and hurtful. Conversely, the headstrong dimension was uniquely associated with hyperactivity ($p < .001$), and the coefficient of association for headstrong was significantly higher compared to irritable and hurtful. Headstrong and hurtful dimensions were equally associated to conduct problems. For prosociality, both headstrong and hurtful dimensions showed a negative significant association.

Using the oppositional dimensions as independent variables and psychiatric disorders as

the outcome, the irritable dimension was uniquely associated with emotional disorders ($p < .001$), any anxiety disorder ($p < .001$), and major depression ($p < .001$), and the odds ratio difference confirmed the finding, with only irritable dimension index being significantly different from the other two. The hurtful dimension showed a significant association with conduct disorder ($p < .05$), but the odds ratio differences with headstrong and irritable dimensions were not significant. As predicted, the headstrong dimension showed a strong association with ADHD ($p < .001$), which was also confirmed by the odds ratio difference, showing a significant difference between headstrong and the other two dimensions. These results are displayed in Table 4.

Our third aim was to examine the association of oppositional dimensions with parental history for individual disorders (Table 5). The irritable dimension showed a specific association with family history of depression ($p < .01$) and suicidality ($p < .05$), whereas headstrong was uniquely associated with family history of childhood ADHD symptoms ($p < .05$). The three ODD dimensions were not associated with family history of drinking, imprisonment, or childhood conduct symptoms.

We repeated all analyses for each stratum (randomized and high-risk) and the results showed the same pattern of results. In particular, the irritable dimension showed strong association with emotional SDQ scores and diagnosis of depression; the headstrong dimension showed an association with ADHD diagnosis; whereas the hurtful dimension showed an association with conduct disorder. The only exception was the association between dimensions and family history; although the odds ratios suggested an association, this was not significant, which may be attributable to limited power after splitting of the sample.

DISCUSSION

This study provides new empirical evidence from a large Brazilian sample on oppositional dimensions model structure and associations with other mental disorders. In particular, the results show the following: first, the model distinguishing among the three dimensions of irritable, headstrong, and hurtful behaviors best fits the data; second, there are distinct associations between each of these three dimensions and other

TABLE 2 Confirmatory Factorial Analysis for Four Different Models of Oppositional Dimensions

Maximum Likelihood	Models of Oppositional Dimensions				
	One-factor (All nine DAWBA Items)	Two-factor Irritable, Headstrong/Hurtful ^a	Three-factor Irritable, Headstrong, and Hurtful ^b	Three-factor Negative Affective, Oppositional, and Antagonistic Behavior ^c	
χ^2	723.705	479.338	133.940	639.140	
Degrees of freedom	27	26	24	24	
AIC	16715.451	16473.084	16131.686	16636.886	
BIC	16854.498	16617.282	16286.183	16791.384	
CFI	0.887	0.926	0.982	0.900	
TLI	0.849	0.898	0.973	0.850	
RMSEA	0.142	0.117	0.060	0.142	
Comparisons	ΔAIC^d	ΔBIC^d	χ^2 Difference	<i>p</i>	
1F vs. 2F	252.267	237.216	244.367(1 d.f.)	<.001	2-factor model better than 1-factor model
1F vs. 3F (irritable, headstrong and hurtful)	583.765	568.315	589.785(3 d.f.)	<.001	3-factor_irritable, headstrong and hurtful better than 1-factor model
2F vs. 3F (irritable, headstrong and hurtful)	361.398	331.099	345.398(2 d.f.)	<.001	3-factor_irritable, headstrong and hurtful better than 2-factor model
1F vs. 3F (negative affective, oppositional behavior and antagonistic behavior)	78.565	63.114	84.565(3 d.f.)	<.001	3-factor _negative affective, oppositional and antagonistic behavior better than 1-factor
2F vs. 3F (negative affective, oppositional and antagonistic behavior)	-163.802	-174.102	Nonnested models		2 factor model better than 3-factor _negative affective, oppositional and antagonistic behavior
3F (negative affective, oppositional and antagonistic behavior) vs. 3F (irritable, headstrong and hurtful)	505.2	505.201	Nonnested models		3-factor_ irritable, headstrong and hurtful better than 3-factor _negative affective, oppositional and antagonistic behavior

Note: 1F = one-factor model; 2F = two-factor model; 3F = three-factor model; AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria; CFI = Comparative Fit Index; DAWBA = Development and Well-Being Assessment; RMSEA = root mean square error of approximation; TLI = Tucker-Lewis Index.

^aModel proposed by Rowe et al.⁷

^bModel proposed by Stringaris et al.¹¹

^cModel proposed by Burke et al.¹⁴

^d ΔAIC and ΔBIC were calculated as the difference between a candidate model and the best (i.e., lowest AIC or BIC model). Values equal to or greater than 10 for ΔAIC and ΔBIC indicate overwhelming support for the lower AIC and BIC models.

TABLE 3 Oppositional Dimensions and Their Associations With the Strengths and Difficulties Questionnaire (SDQ)

Oppositional dimensions	SDQ				
	Emotional Problems	Hyperactivity	Conduct Problems	Peer Problems	Prosociality
Irritable	0.73 (0.52, 0.94)***	0.03 (−0.17, 0.24)	−0.01 (−0.14, 0.12)	0.08 (−0.09, 0.26)	0.05 (−0.10, 0.21)
Headstrong	0.04 (−0.17, 0.26)	0.86 (0.64, 1.08)***	0.62 (0.48, 0.77)***	0.28 (0.09, 0.47)**	−0.38 (−0.54, −0.21)***
Hurtful	0.03 (−0.13, 0.21)	−0.009 (−0.18, 0.16)	0.32 (0.21, 0.44)***	0.26 (0.11, 0.42)**	−0.19 (−0.32, −0.06)**
Comparisons	Irr Head Hurt	Head Irr Hurt	Irr Head Hurt	Irr Head Hurt	Irr Head Hurt

Note: Values correspond to standardized coefficients of multivariate linear regression models (with the three dimensions as independent variables controlled for age and gender) and their 95% confidence interval in parentheses for the oppositional dimensions. Bottom row shows comparison between individual coefficients for each oppositional dimension of symptoms, testing the null hypothesis that they not differ. Coefficients underlined are not significantly different at the level of $p < .05$. Head = headstrong; Hurt = hurtful; Irr = irritable.

** $p \leq .01$; *** $p \leq .001$.

TABLE 4 Oppositional Dimensions and Their Associations With Psychiatric Diagnosis

Oppositional dimensions	Psychiatric Diagnosis				
	Emotional Disorders	Any anxiety Disorder	Major Depression	Conduct Disorder	ADHD
Irritable	1.9 (1.5, 2.3)***	1.6 (1.3, 2.0)***	2.7 (1.8, 4.1)***	1.3 (0.84, 2.3)	0.94 (0.76, 1.1)
Headstrong	0.97 (0.78, 1.2)	1.0 (0.79, 1.2)	0.89 (0.61, 1.3)	1.5 (0.97, 2.5)	2.6 (2.0, 3.2)***
Hurtful	1.0 (0.88, 1.2)	0.96 (0.81, 1.1)	1.1 (0.94, 1.4)	1.3 (1.0, 1.8)*	1.0 (0.90, 1.2)
Comparisons	Irr Head Hurt	Irr Head Hurt	Irr Head Hurt	Irr Head Hurt	Head Irr Hurt

Note: Values correspond to standardized odds ratios of multivariate logistic regression models (with the three dimensions as independent variables controlled for age and gender) and their 95% confidence interval in brackets for the oppositional dimensions. The comparison column shows contrasts between individual odds ratios, testing the null hypothesis that they do not differ, and those with common underlining are not significantly different at the level of $p < .05$. Emotional disorders includes both depressive and anxiety disorders. ADHD = attention-deficit/hyperactivity disorder; Head = headstrong; Hurt = hurtful; Irr = irritable.

* $p \leq .05$; *** $p \leq .001$.

TABLE 5 Oppositional Dimensions and Their Associations With Parental History of Psychopathology

Oppositional dimensions	Parental History of Psychopathology					
	Depression	Suicidality	History of ADHD Symptoms	Drinking	History of Conduct Symptoms	Imprisonment
Irritable	1.3 (1.1, 1.5)**	1.2 (1.0, 1.4)*	1.0 (0.83, 10.2)	0.97 (0.76, 1.2)	1.0 (0.85, 1.2)	0.98 (0.73, 1.3)
Headstrong	1.1 (0.96, 1.3)	1.1 (0.90, 1.3)	1.3 (1.0, 1.6)*	1.1 (0.92, 1.5)	1.0 (0.86, 1.2)	1.0 (0.75, 1.3)
Hurtful	1.0 (0.94, 1.2)	1.1 (0.95, 1.2)	0.92 (0.77, 1.0)	1.0 (0.82, 1.2)	1.0 (0.91, 1.2)	1.1 (0.92, 1.4)
Comparisons	<u>Irr Head Hurt</u>	<u>Irr Head Hurt</u>	<u>Head Irr Hurt</u>	<u>Irr Head Hurt</u>	<u>Irr Head Hurt</u>	<u>Irr Head Hurt</u>

Note: Values correspond to standardized odds ratios of multivariate logistic regression models (with the three dimensions as independent variables controlled for age and gender) and their 95% confidence interval in brackets for the oppositional dimensions. Comparison column shows contrasts between individual odds ratios, testing the null hypothesis that they do not differ, those with common underlining are not significantly different at the level of $p < .05$. ADHD = attention-deficit/hyperactivity disorder; Head = headstrong; Hurt = hurtful; Irr = irritable.
* $p \leq .05$; ** $p \leq .01$.

psychiatric disorders, consistent with previous studies from European and US samples; and third, the oppositional dimensions show a distinct association with family risks, in keeping with hypotheses about distinct etiological processes for each of the dimensions.

The first aim of this article was to compare models that distinguish between dimensions of oppositionality. We found that the model containing irritable, headstrong, and hurtful dimensions, as initially identified by Stringaris *et al.*,¹¹ fit the data best compared with the two-factor model (irritable, headstrong/hurtful) and the three-factor model proposed by Burke *et al.*, (negative affective, oppositional behavioral, and antagonistic behavior),¹⁴ as indicated by comparative and absolute fit indices. These results support the current division of oppositional dimensions suggested by the DSM-5 Taskforce in their proposal.

To our knowledge, this is the first study to test the dimensional structure of oppositionality through confirmatory factorial analysis, outside Europe and the United States. In our Brazilian sample, we found a structure similar to those suggested in previous studies,^{11,12} with distinct associations for each of the dimensions. As previously shown, the irritable dimension was strongly correlated with emotional symptoms and emotional disorders; headstrong was strongly associated with SDQ hyperactivity scores and a diagnosis of ADHD, whereas hurtful showed a strong association either with conduct symptoms on SDQ or conduct disorder. This constellation of findings suggests that dimensions of oppositionality may not be a phenomenon restricted to a particular geographic location or

cultural background. Previous studies have suggested that differences in the prevalence or pattern of symptoms between countries may be due to methodological factors rather than geographic or cultural factors.^{35,36} In any case, it is important to examine for overlaps and differences in the constellation of psychiatric symptoms and disorders outside the United States or Europe, not least because 90% of children's world population comes from low- and middle-income countries. As the DSM is being used worldwide, it is reassuring to find that the proposed changes for oppositionality may apply outside the United States.³⁷

Our third aim was to examine specific associations between dimensions of oppositionality and parental history of psychopathology. We found a differential association between the irritable dimension and a family history of depression and suicidality. This is in keeping with previous findings concerning shared genetic risk factors between irritability and depression.^{15,38} It also demonstrates the close links between irritability and suicidal behaviors, as indicated in previous research.³⁹ It is unclear what the mechanisms of shared risks between irritability and depression are. It is possible that altered affect regulation processes play a key role. For example, a reduced volume of the right dorso-lateral prefrontal cortex (DLPFC)^{40,41}—an area implicated in behavior and affective processing—is found both in children with severe irritability as well as in the offspring of mothers with depression. In keeping with our expectations, we found that childhood headstrong behavior shares familial risks with parental history of ADHD symptoms during childhood.

Little is known at present about what the shared mechanisms between headstrong and ADHD could be. It is possible that higher levels of cognitive impulsivity are common to both presentations, and further research is required to test this assumption. The hurtful dimension showed a specific association with conduct disorder and SDQ conduct scores. However, contrary to our prediction, we did not find an association between the hurtful dimension and a family history of imprisonment and antisocial behavior, although a true association might have been masked by the low overall prevalence of imprisonment or by selective under-reporting of socially undesirable outcomes. Future studies that will include callous and unemotional traits as an outcome might be more informative in this regard.⁴²

Our study should be seen in the light of its limitations. First, the sample is not representative of the full ethnic diversity of the Brazilian population, so its results may not generalize to all sectors of society. In addition, the majority of those in the ODD dimensions subsample (those who screened positively) were from the high-risk sample, and this may limit the generalizability of our findings. Second, the evaluation was performed with only one of the parents and did not include other reporting sources. Third, the family history information was gathered retrospectively and is therefore liable to recall bias (although there is no obvious reason why this could have had differential effects on the three dimensions). Fourth, the reader should note that the hurtful model—which has only two indicators—would be under-identified in a model without any other latent variables.⁴³ Future instruments should test models with more item indicators for this dimension, to increase the reliability of the latent trait model. Finally, at this point in time, our data are cross-sectional, limiting the strength of causal inferences; future studies using longitudinal data should re-examine the hypotheses tested here, possibly by using a structural equation modeling framework.

Our study has implications for researchers and clinicians. Our findings lend empirical support for a nosological model for *DSM-5* and other classifications. For research, our data extend previous findings on oppositional dimensions by identifier distinct familial associations. Clinicians may need to particularly assess one or another type of clinical correlates and possibly develop differentiated treatments according to the

relative balance of irritable, headstrong, and hurtful dimensions.

In summary, our findings from a large community sample of Brazilian children support a distinction between dimensions of oppositionality, and provide further evidence for etiological distinction between dimensions. &

Clinical Guidance

- Youth with oppositional defiant disorder (ODD) have a higher risk for a wide range of other psychiatric problems, including antisocial outcomes, attention-deficit/hyperactivity disorder (ADHD) as well as depression.
- Three different dimensions within oppositionality, termed irritable, headstrong, and hurtful, explain why there is such a wide range of ODD outcomes.
- Here we show in an independent sample from Brazil how these dimensions are differentially associated with psychiatric outcomes: irritable showed a differentially strong link with emotional and depressive disorders; headstrong with ADHD and hurtful with conduct disorder.
- In addition, we show that these different associations may be explained by family history: irritable is differentially linked to maternal depression; and headstrong with parental history of ADHD symptoms.
- Our findings lend further support for the *DSM-5* decision to distinguish between three dimensions of oppositionality in youth.

Accepted January 11, 2013.

Drs. Krieger and Graeff-Martins are with the University of São Paulo. Drs. Krieger, Goodman, Stahl, and Stringaris are with the Institute of Psychiatry at King's College London. Drs. Polanczyk, Rohde, Salum, Graeff-Martins, Gadelha, and Pan are with the National Institute of Developmental Psychiatry for Children and Adolescents (INCT-CNPq), Brazil. Dr. Polanczyk is with the Research Support Center on Neurodevelopment and Mental Health at the University of São Paulo. Drs. Rohde and Salum are with the Federal University of Rio Grande do Sul, Brazil. Dr. Pan is with the Federal University of São Paulo.

This work is supported by the following Brazilian government agencies: the National Council for Scientific and Technological Development (CNPq), the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), and the São Paulo Research Foundation (FAPESP).

Dr. Krieger served as the statistical expert for this research.

The authors thank the children and families for their participation, which made this research possible.

Disclosure: Dr. Polanczyk has served as a speaker and/or consultant to Eli Lilly and Co., Novartis, Janssen-Cilag, and Shire Pharmaceuticals; has developed educational material to Janssen-Cilag; and has received unrestricted research support from Novartis and CNPq. Dr. Goodman is the owner of Youthmind, which provides no-cost and low-cost software and websites related to the Strengths and Difficulties Questionnaire (SDQ) and the Development and Well-Being Assessment (DAWBA). Dr. Rohde has served as a consultant to, on the speakers' bureau for, and/or on the advisory board for Eli Lilly and Co., Janssen-Cilag, Novartis, and Shire. He has received royalties from Artes

Médicas and Oxford University Press. He is the chair of the Attention-Deficit/Hyperactivity Disorder and Juvenile Bipolar Disorder Out-patient Programs, which have received unrestricted educational and research support from Abbott, Eli Lilly and Co., Janssen-Cilag, Novartis, and Shire. Dr. Gadelha has received payment for the development of educational material for Janssen-Cilag, AstraZeneca, and Eli Lilly and Co., and has received meeting payment expenses from Eli Lilly and Co. and Janssen-Cilag. Dr. Pan has received payment for development of educational material for Janssen-Cilag and AstraZeneca; and has received meeting payment expenses from Eli Lilly and Co. Dr. Stringaris has received support from the Wellcome Trust and the

U.K. Department of Health. Drs. Krieger, Graeff-Martins, Salum, and Stahl report no biomedical financial interests or potential conflicts of interest.

Correspondence to: Fernanda Valle Krieger, M.D., University of São Paulo, Institute of Psychiatry - R., Dr. Ovídio Pires de Campos, 785, 1° andar, sala 1C 015 Postcode: 05403-903, São Paulo - SP - Brazil; e-mail: fvkrieger@gmail.com

0890-8567/\$36.00/© 2013 American Academy of Child and Adolescent Psychiatry

<http://dx.doi.org/10.1016/j.jaac.2013.01.004>

REFERENCES

- Stringaris A, Maughan B, Goodman R. What's in a disruptive disorder? Temperamental antecedents of oppositional defiant disorder: findings from the Avon longitudinal study. *J Am Acad Child Adolesc Psychiatry*. 2010;49:474-483.
- American Psychiatric Association. *DSM-5: The Future of Psychiatric Diagnosis* 2012. Available at: <http://www.dsm5.org/ProposedRevision/Pages/proposedrevision.aspx?rid=106>. Accessed November 4, 2012.
- American Psychiatric Association. *Diagnostic and Statistics Manual of Mental Disorders, 4th Edition (DSM-IV)*. Washington, DC: American Psychiatric Association; 1994.
- Costello EJ, Mustillo S, Erkanli A, Keeler G, Angold A. Prevalence and development of psychiatric disorders in childhood and adolescence. *Arch Gen Psychiatry*. 2003;60:837-844.
- Maughan B, Rowe R, Messer J, Goodman R, Meltzer H. Conduct disorder and oppositional defiant disorder in a national sample: developmental epidemiology. *J Child Psychol Psychiatry*. 2004;45:609-621.
- Boylan K, Vaillancourt T, Boyle M, Szatmari P. Comorbidity of internalizing disorders in children with oppositional defiant disorder. *Eur Child Adolesc Psychiatry*. 2007;16:484-494.
- Rowe R, Maughan B, Pickles A, Costello EJ, Angold A. The relationship between DSM-IV oppositional defiant disorder and conduct disorder: findings from the Great Smoky Mountains Study. *J Child Psychol Psychiatry*. 2002;43:365-373.
- Rowe R, Maughan B, Costello EJ, Angold A. Defining oppositional defiant disorder. *J Child Psychol Psychiatry*. 2005;46:1309-1316.
- Copeland WE, Shanahan L, Costello EJ, Angold A. Childhood and adolescent psychiatric disorders as predictors of young adult disorders. *Arch Gen Psychiatry*. 2009;66:764-772.
- Kim-Cohen J, Caspi A, Moffitt TE, Harrington H, Milne BJ, Poulton R. Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. *Arch Gen Psychiatry*. 2003;60:709-717.
- Stringaris A, Goodman R. Three dimensions of oppositionality in youth. *J Child Psychol Psychiatry*. 2009;50:216-223.
- Stringaris A, Goodman R. Longitudinal outcome of youth oppositionality: irritable, headstrong, and hurtful behaviors have distinctive predictions. *J Am Acad Child Adolesc Psychiatry*. 2009;48:404-412.
- Aebi M, Muller UC, Asherson P, et al. Predictability of oppositional defiant disorder and symptom dimensions in children and adolescents with ADHD combined type. *Psychol Med*. 2010;40:2089-2100.
- Burke JD, Hipwell AE, Loeber R. Dimensions of oppositional defiant disorder as predictors of depression and conduct disorder in preadolescent girls. *J Am Acad Child Adolesc Psychiatry*. 2010;49:484-492.
- Stringaris A, Zavos H, Leibenluft E, Maughan B, Eley TC. Adolescent irritability: phenotypic associations and genetic links with depressed mood. *Am J Psychiatry*. 2012;169:47-54.
- Rowe R, Costello EJ, Angold A, Copeland WE, Maughan B. Developmental pathways in oppositional defiant disorder and conduct disorder. *J Abnorm Psychol*. 2010;119:726-738.
- Ezpeleta L, Granero R, de la Osa N, Penelo E, Domenech JM. Dimensions of oppositional defiant disorder in 3-year-old pre-schoolers. *J Child Psychol Psychiatry*. 2012;53:1128-1138.
- Wakschlag LS, Henry DB, Tolan PH, Carter AS, Burns JL, Briggs-Gowan MJ. Putting theory to the test: modeling a multidimensional, developmentally-based approach to preschool disruptive behavior. *J Am Acad Child Adolesc Psychiatry*. 2012;51:593-604.
- Bornova MA, Hicks BM, Iacono WG, McGue M. Familial transmission and heritability of childhood disruptive disorders. *Am J Psychiatry*. 2010;167:1066-1074.
- Meadows S, Lanahan MC, Brooks-Gunn S J. Parental Depression and Anxiety and Early Childhood Behavior Problems Across Family Types. *J Marriage Fam*. 2007;69:1162-1177.
- Barker ED, Copeland W, Maughan B, Jaffee SR, Uher R. Relative impact of maternal depression and associated risk factors on offspring psychopathology. *Br J Psychiatry*. 2012;200:124-129.
- Kim-Cohen J, Moffitt TE, Taylor A, Pawlby SJ, Caspi A. Maternal depression and children's antisocial behavior: nature and nurture effects. *Arch Gen Psychiatry*. 2005;6:173-181.
- Salum GA, Mogg K, Bradley BP, et al. Threat bias in attention orienting: evidence of specificity in a large community-based study. *Psychol Med*. 2012;1-13.
- Weissman MM, Wickramaratne P, Adams P, Wolk S, Verdelli H, Olfson M. Brief screening for family psychiatric history: the family history screen. *Arch Gen Psychiatry*. 2000;57:675-682.
- Goodman R. The Strengths and Difficulties Questionnaire: a research note. *J Child Psychol Psychiatry*. 1997;38:581-586.
- Goodman R. Psychometric properties of the strengths and difficulties questionnaire. *J Am Acad Child Adolesc Psychiatry*. 2001;40:1337-1345.
- Goodman R, Ford T, Richards H, Gatward R, Meltzer H. The Development and Well-Being Assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology. *J Child Psychol Psychiatry*. 2000;41:645-655.
- Goodman A, Fleitlich-Bilyk B, Patel OSC. Child, family, school and community risk factors for poor mental health in Brazilian school-children. *J Am Acad Child Adolesc Psychiatry*. 2007;46:448-456.
- Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59(Suppl 20):22-33. quiz 34-57.
- Hooper DCJ, Mullen M. Structural equation modelling: guidelines for determining model fit. *Electron J Bus Res Methods*. 2008;6:53-60.
- Levy RHG. A framework of statistical tests for comparing mean and covariance structure models. *Multivar Behav Res*. 2007;42:33-66.
- Burnham KPAD. Multimodel inference-understanding AIC and BIC in model selection. *Sociol Methods Res*. 2004;33:261-304.
- Muthen LK, Muthen BO. *Mplus User's Guide*, 5th ed. Los Angeles, CA; 2007.
- StataCorp. *Stata Statistical Software: Release 10.0*. College Station, TX: Stata Corporation LP 2007.
- Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and meta-regression analysis. *Am J Psychiatry*. 2007;164:942-948.
- Rescorla L, Achenbach TM, Ivanova MY, et al. Epidemiological comparisons of problems and positive qualities reported by adolescents in 24 countries. *J Consult Clin Psychol*. 2007;75:351-358.

37. Kieling C, Baker-Henningham H, Belfer M, *et al.* Child and adolescent mental health worldwide: evidence for action. *Lancet*. 2011;378:1515-1525.
38. Leibenluft E. Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. *Am J Psychiatry*. 2011;168:129-142.
39. Pickles A, Aglan A, Collishaw S, Messer J, Rutter M, Maughan B. Predictors of suicidality across the life span: the Isle of Wight study. *Psychol Med*. 2009;40:1453-1466.
40. Amico F, Meisenzahl E, Koutsouleris N, Reiser M, Moller HJ, Frodl T. Structural MRI correlates for vulnerability and resilience to major depressive disorder. *J Psychiatry Neurosci*. 2011;36:15-22.
41. Adleman NE, Fromm SJ, Razdan V, *et al.* Cross-sectional and longitudinal abnormalities in brain structure in children with severe mood dysregulation or bipolar disorder. *J Child Psychol Psychiatry*. 2012;53:1149-1156.
42. Fontaine NM, Rijdsdijk FV, McCrory EJ, Viding E. Etiology of different developmental trajectories of callous-unemotional traits. *J Am Acad Child Adolesc Psychiatry*. 2010;49:656-664.
43. Kenny DA. SEM: Identification. 2011. Available at: <http://davidakenny.net/cm/identify.htm>. Accessed November 5, 2012.

FIGURE S1 Models of oppositionality. Note: DAWBA = Development and Well-Being Assessment; ODD = oppositional defiant disorder. ^aModel proposed by Rowe *et al.* ^bModel proposed by Stringaris *et al.* ^cModel proposed by Burke *et al.*

SUPPLEMENTAL REFERENCES

1. Rowe R, Maughan B, Costello EJ, Angold A. Defining oppositional defiant disorder. *J Child Psychol Psychiatry*. 2005;46:1309-1316.
2. Stringaris A, Goodman R. Three dimensions of oppositionality in youth. *J Child Psychol Psychiatry*. 2009;50:216-223.
3. Burke JD, Hipwell AE, Loeber R. Dimensions of oppositional defiant disorder as predictors of depression and conduct disorder in preadolescent girls. *J Am Acad Child Adolesc Psychiatry*. 2010; 49:484-492.

5.2.1 Discussão Artigo 2

Nos últimos anos inúmeros estudos propuseram que o diagnóstico de Transtorno de Oposição e Desafio (TOD) era composto por distintas dimensões de psicopatologia. Este é o primeiro estudo a validar as distintas dimensões subjacentes ao diagnóstico de TOD fora do eixo Europa - Estados Unidos.

O primeiro objetivo do estudo comparou os diferentes modelos de estruturação das dimensões subjacentes ao TOD. O modelo contendo os 3 fatores, “Irritable”, “Headstrong”, “Hurtful” demonstrou o melhor ajuste para os dados da amostra brasileira, corroborando o modelo incorporado pelo DSM-5.

Revalidando estudos prévios, a dimensão “Irritable” se associou a sintomas e transtornos emocionais; enquanto a dimensão “Headstrong” esteve correlacionada com TDAH. A dimensão “Hurtful” esteve associada com transtorno de conduta (TC).

Além disso, encontramos uma associação entre a dimensão “Irritable” e história familiar de depressão e suicidalidade, sugerindo diferentes etiologias para cada dimensão.

5.3 Artigo 3

“Testing irritability under RDoC framework: evidence from two large and culturally distinct epidemiological samples”

Testing irritability under RDoC framework: evidence from two large and culturally distinct epidemiological samples

Krieger, F.V; Polanczyk, G.V; Goodman, R.; Stringaris, A.

Irritability is one of most common features in child psychiatry and it is associated with significant psychosocial impairment and a predictor of depressive symptoms(1). Present across multiple diagnoses and reflecting an excessive reactivity to negative emotional stimuli, irritability varies in intensity, from mild annoyance to disproportionate aggression or rage (2). As a dimensional trait underlying distinct disorders, irritability fits under the National Institute of Mental Health Research Domain Criteria (RDoC) framework (3) that proposes a new way of understanding mental illness through dimensional constructs underlying observable behavior. Applying the RDoC perspective in two large and culturally distinct epidemiological samples from UK and Brazil, we examine the impact and longitudinal outcomes of irritability across diverse clinical pictures.

Clinically displayed as easy annoyance, touchiness and temper outbursts, irritability has been studied in a variety of clinical settings (4-7). In individuals with ADHD, disproportionate emotional reactivity is seen in approximately 40% of cases and is associated with additional impairment, depressive and disruptive comorbid disorders and persistence of ADHD symptoms across time (8-11). Similarly, irritability is highly prevalent in anxiety disorders where it is associated with greater severity of symptoms, poorer quality of life and suicidal ideation (12, 13). In young people with obsessive-compulsive disorder (OCD), temper outbursts is two to three times more common than in healthy subjects, and once again, it is significantly associated to higher impact scores and depressive symptoms (14). Furthermore, a third of youths diagnosed with depression also exhibit irritability, which increases rates of comorbid disruptive disorders (15).

Indeed, empirical evidence so far supports an association of irritability with increased impairment and depressive symptoms. Depression and anxiety are the most likely longitudinal outcomes of children with significant irritability in community

samples, and shared common genes are suggested to underlie both conditions (1, 16-18). Besides, maternal depression is associated with irritability trajectories at early ages (19, 20). However, although significant irritability associates to additional psychosocial impairment and depressive symptoms in specific samples, it is not clear whether it leads to similar outcomes across distinct clinical pictures. In other words, it should be investigated whether the impact of irritability varies according to the underlying condition.

Irritability fits well within RDoC initiative, which proposes that psychopathology should be addressed through underlying constructs rather than discrete diagnostic categories (21). The principles of RDoC encompass irritability: First, it calls for a dimensional rather than a diagnostic or categorical system. Second, rather than beginning with a diagnostic group and attempting to discover its neurobiological basis, RDoC begins with underlying constructs and relates these to clinical phenomenology.

A more thorough understanding of mental disorders in children depends upon analyses of data drawn from epidemiological samples, encompassing major cultural and socio-economic diversity. The current scenario falls clearly short of this as available data derive from clinical settings in developed countries. Epidemiological samples are less prone to referral and Berkson biases, an important advantage when addressing issues of comorbidity (22). Furthermore, examining culturally distinct samples may allow a more reliable verification of the robustness and universality of constructs, thus enhancing the ability to predict outcomes.

Using two large samples, from UK and Brazil we examine dimensional irritability outcomes in each of the following scenarios: 1. subjects with a diagnosis of ADHD; 2. subjects with emotional disorders (i.e. depression and/or anxiety); 3. healthy subjects, without any diagnosis.

Specifically, we investigate the impact and longitudinal outcomes of irritability across these three groups. Our hypothesis is that dimensional irritability will confer additional psychosocial impairment regardless diagnosis status. Besides, because irritability is associated with depression and anxiety, we hypothesized that it will increase the risk of emotional disorders through development. To ensure that findings are not driven by comorbidity with oppositional defiant disorder (ODD), we exclude from the analyses subjects with this diagnosis.

Methods

Samples

UK sample: The British Child and Adolescent Mental Health Survey (B-CAMHS) is a longitudinal cohort, representative of the general British population, that included 7977 children from 5 to 16 years old(23). The study used “child benefit” (a universal state benefit payable in Great Britain for each child in a family) to develop a sampling frame in different postal sectors in England, Wales, and Scotland. Of the 12294 contacted, 10496 were approached in person. Of those, 7977 were included at baseline evaluation. Follow-up assessments were carried out at 12, 24 and 36 months. At baseline and 36-month follow-up, families were approached personally, whereas at 12 and 24-month assessments, parents who had agreed to be followed up were mailed a Strengths and Difficulties Questionnaire (SDQ). Of the original 7977, 6375 children (79%) participated at 12-month follow-up, 5794 (72%) at 24-month, and 5325 (66 %) at 36-month follow-up (24). Attrition analysis showed that those with missing data at 36-month follow-up (n=2652) did not differ by gender, but were more likely to be older (mean= 10.9 SD 3.4 vs. mean=10.3 SD 3.3; $p<0.001$), suffer from a psychiatric disorder (13% vs. 8%; $p<0.001$), and belong to families living in rented homes (39% vs. 23%; $p<0.001$). The sampling design, interviewing procedures, information leaflets and interview schedules were approved by The Central Office for Research Ethics Committees (COREC) of the UK. Children provided assent for their own participation but did not have a veto over their parent’s participation on the basis of their own informed consent.

Brazilian sample: The Braziliancommunity school-based study is a cross sectional study of 2512 children aged 6 to 12 years that was carried out in Porto Alegre and São Paulo(25). Participants underwent psychiatric, genetic, neuroimaging and neuropsychological evaluations. Sampling included several steps: a screening phase in 57 public schools, where 9937 informants responded to the Family History Survey (26). From these, two groups were selected, a random stratum, where a simple randomization was used, and an ‘at-risk’ stratum, where a risk prioritization-based procedure selected individuals with a family history and/or ongoing symptoms on one of five target domains (ADHD, anxiety, obsessive-compulsive disorder, psychosis and learning disorders). From 1315 children selected in the random stratum, 958 (73%) completed evaluation. There were no differences in gender, but those who participated in the study

were younger (mean=8.6, SD 1.8 vs. mean=9.1, SD 1.9; $p<0.001$). From the 2050 children of the ‘at-risk’ group, 1554 (76%) participated in the study, and attrition analyses showed no differences in age or gender. The total sample comprised 2512 children who verbally assented to participate and whose parents provided written consent. When appropriate, written assent was also obtained. The study was approved by the ethics committee of the University of São Paulo (IORG0004884, project IRB registration number: 1132/08).

Participants

Samples are summarized on table 1. Individuals pertaining to the UK sample were older (UK: 10.5 years, 95% CI 10.4, 10.6 *versus* Brazil: 9.7, 95% CI 9.6, 9.7), more likely to be white (UK: 86.7%, 95% CI 86, 87.4 *versus* Brazil: 60.6%, 95% CI 58.7, 62.5) and more likely to have a mother with graduation degree (UK: 26.7%, 95% CI 25.7, 27.7 *versus* Brazil: 3.4%, 95% CI 2.7, 4.1). In both samples participants were divided into 3 groups: those with ADHD, those with any emotional disorder and those with no DSM-IV specific diagnosis according to DAWBA.

Of the 7977 participants in the UK sample, 89 had ADHD, 224 emotional disorders and 7213 had no diagnosis. Eight subjects had comorbid ADHD and emotional disorder and were included in both groups. Those with emotional disorders were older, whereas the ADHD group showed a higher proportion of males. Two-hundred and five children in the Brazilian sample had ADHD, 304 emotional disorders and 1860 did not meet criteria for any diagnosis. Forty-six had comorbid ADHD and emotional disorder and were included in both groups. There was no difference in age, ethnicity and maternal education between groups. A higher proportion of males were observed in ADHD compared to emotional disorders group.

In the UK sample, 156 subjects with comorbid ODD were excluded (87 with ADHD and 69 with emotional disorders). In the Brazilian sample, 100 subjects with ODD were excluded (69 with comorbid ADHD and 31 with emotional disorders).

Measurements

Strengths and Difficulties Questionnaire (SDQ)(27): This is a 25-item questionnaire comprising five symptom domains (emotional problems, hyperactivity, conduct problems, peer problems, prosociality) and an impact score that evaluates distress and psychosocial impairment (28). High reliability and validity suggests it is a good measure of psychopathology adjustment in children and adolescents (29). The parental

version of the SDQ was used, although youth and teacher versions are also available. In the UK sample, SDQ was applied at baseline, 12, 24 and 36-month follow-up, whereas in the Brazilian sample it was applied at baseline. SDQ scores measured impairment and morbidity, and served as dependent variables for irritability predictions.

Development and Well-Being Assessment (DAWBA)(30): This is a structured interview administered by lay interviewers who also record the verbatim accounts of any reported problems. The questions are closely related to DSM-IV and ICD-10 diagnostic criteria and focus on current problems. The DAWBA has skip rules that allow interviewers to omit many detailed questions in a section when the preliminary answer indicates a very low probability of disorder in that domain. It was applied at baseline in the Brazilian sample, and at baseline and 36-month follow-up in the UK sample. DSM-IV diagnoses and irritability variable were derived from DAWBA.

Indicators of psychosocial impairment: Information on self-harm, truancy, contact with police and use of mental health services was part of baseline and 36-month follow-up evaluations in the UK sample. A participant was coded as having experienced one of these outcomes if so rated by youth, teacher or parent report. For self-harm, information was only available from youth and parents. To address predictive validity, we examined whether baseline irritability predicted new onset of self-harm, truancy, contact with police and use of mental health services over follow-up.

Assessment of irritability

We defined irritability as the irritable dimension of ODD, that derives from a cluster of ODD symptoms and has been extensively described and validated in children and adolescents (31)(16)(19)(18)(2). Briefly, those who responded affirmatively to DAWBA's ODD skip question ("*child is more troublesome than others at same age?*") were asked nine questions based on DSM-IV ODD diagnosis. The irritable dimension was composed by three items: first, "*had temper outbursts?*"; second, "*been touchy and easily annoyed?*"; and third, "*been angry and resentful?*". Response scores were "no more than others" (0), "a little more than others" (1), and "a lot more than others"(2). In both samples, irritable dimension was composed by the sum of each item score and ranged from 0 ("no more than others" in all three items) to 6 ("a lot more than others" in all three items). Individuals who responded negatively to DAWBA's ODD skip question were considered as scoring zero in all three items(UK: n= 6201; Brazil: n=1238). Irritability was used as the main predictor throughout the study. In order to

avoid confusion bias and to reassure that irritability predictions were not driven by ODD diagnosis, individuals with ODD were excluded from main analyses. According to DSM-5, ODD diagnosis is given when at least 4 of 8 core symptoms (including those 3 items for irritability) are present (32).

Statistical Analyses

Irritability rates were estimated through the mean of scores of the irritable dimension (minimum 0, maximum 6) and one-way ANOVA was conducted to compare rates between groups. Linear regression models were performed for each group separately using cross sectional SDQ scores as dependent variables and irritability as predictor in both samples. Linear mixed effect models, adjusted for time and time versus irritability interaction, were conducted to examine the impact of irritability on SDQ scores over time in the UK sample. Logistic regression models were performed using longitudinal DSM-IV diagnoses (ADHD and conduct disorder, any emotional disorder, any disorder at 3-year follow-up) and longitudinal psychosocial indicators (self harm, truancy, police contact and use of mental health services at 3-year follow-up) as dependent variables and baseline irritability as predictor. When needed, repeated analyses including subjects with ODD were performed (appendix 2).

All analyses were adjusted for age and gender. Standardized coefficients and odds ratios are reported for linear and logistic models, respectively. Standardized coefficients with 95% confidence interval were reported for linear mixed effect models. An alpha level of 0.05, two-tailed, was considered significant. Analyses were performed using Stata version 12 (33).

Results

Irritability scores

Irritability was significantly higher in the Brazilian sample (mean .69; 95% CI .60, .78), even when analyses were restricted to those randomly selected (BR: mean .35; 95% CI .29, .42; UK: mean .17; 95% CI .16, .19). In both samples, irritability was significantly lower in those without any disorder compared to children with ADHD and those with emotional disorders, whereas the latter two showed overlapping rates (table 1).

Impact of irritability on cross sectional SDQ scores in both samples

Table 2 displays standardized coefficients of associations between irritability and SDQ scores in both samples. Irritability predicted an overall increase in cross sectional SDQ scores irrespective of underlying condition. In both samples and in all groups, irritability was strongly associated with emotional ($p < .01$) and conduct problems ($p < .001$), impact scores ($p < .01$), and SDQ total scores ($p < .001$). The only exception was Brazilian ADHD group in which higher irritability scores did not translate into more hyperactivity symptoms. Comparisons between groups showed that coefficients of association were significantly stronger (i.e. did not overlap) in controls compared to those with ADHD or emotional disorders for hyperactivity and total scores in the UK, and for emotional, conduct and total scores in the Brazilian sample. In contrast, coefficients of association overlapped between ADHD and emotional disorders groups throughout SDQ scores in both samples. Fitted regression models are displayed in figure 1.

Table 2. Irritability predictions on cross sectional SDQ scores across groups in both samples

Cross sectional SDQ scores	UK sample			Brazilian sample		
	ADHD	Emotional disorders	No disorder	ADHD	Emotional disorders	No disorder
Emotion	.24(.07, .40)**	.25(.14, .37)***	.29(.26, .33)***	.17(.09, .25)***	.13(.07, .19)***	.36(.31, .41)***
Conduct	.54(.40, .67)***	.40(.32, .48)***	.67(.64, .70)***	.23(.15, .31)***	.37(.31, .43)***	.58(.53, .62)***
Hyperactivity	.13(.03, .23)**	.16(.07, .23)**	.38(.35, .41)***	.02(-.03, .07)	.21(.14, .27)***	.37(.32, .42)***
Impact	.44(.21, .67)***	.27(.09, .46)**	.24(.22, .26)***	.26(.15, .37)***	.33(.24, .42)***	.18(.14, .21)***
Total	.37(.25, .49)***	.33(.23, .43)***	.53(.50, .56)***	.18(.12, .24)***	.27(.22, .33)***	.51(.47, .56)***

Values correspond to standardized coefficients of linear regression models (with irritability as independent variable and adjusted for age and gender) and their 95% confidence interval in parentheses for cross sectional SDQ scores. * $p \leq .05$; ** $p \leq .01$; *** $p \leq .001$

Table 1. Description of the samples and scores of irritability

	UK sample					Brazilian sample				
	Whole sample	ADHD ^a	Emotional disorders ^b	No disorder ^c	p ≤.05	Whole sample	ADHD ^a	Emotional disorders ^b	No disorder ^c	p ≤.05
n	7977	89	224	7213		2512	205	304	1860	
Age Mean (SD)	10.5 (3.3)	10.2 (3.3)	12.0 (3.1)	10.4 (3.4)	b > a b > c	9.7 (1.9)	9.6 (1.7)	9.8 (1.9)	9.6 (1.9)	NS
Gender Male	51.5%	84.2%	39.2%	50.4%	a > b a > c c > b	53.1%	60.9%	48.3%	52.3%	a > b
Ethnicity White	86.7%	88.7%	87.5%	86.4%	NS	60.6%	59.8%	63.6%	60%	NS
Maternal education Degree	26.7%	22.0%	15.2%	27.7%	c > b	3.4%	6.9%	4.3%	3.1%	NS
Irritability Mean (95% CI)	.38 (.35, .40)	1.4(1.1, 1.8)	.95 (.75, 1.1)	.17 (.16, .19)	a > c b > c a = b	.91 (.85, .97)	1.9(1.7, 2.2)	1.6(1.4, 1.9)	.47 (.42, .51)	a > c b > c a = b

^a subjects with attention deficit hyperactivity disorder excluding those with comorbid oppositional defiant disorder; ^b subjects with emotional disorders excluding those with comorbid oppositional defiant disorder

^c subjects without any disorder. p ≤.05= groups significantly different at the level of p ≤.05. NS= non significant.

Figure 1. Fitted regression of irritability on cross sectional SDQ scores by group in both samples

UK= UK sample; BR= Brazilian sample; ADHD= attention deficit hyperactivity disorder

Graphs on the left illustrate findings in the UK and those on the right in the Brazilian sample. Note that in all measures of associations with symptoms and impact, the greater the irritability score, the higher the morbid association – with the exception of hyperactivity in the Brazilian sample (third graph on the right).

Impact of irritability on SDQ scores over time in the UK sample

Linear mixed effect models were performed to probe for the impact of irritability over the years. Results from linear mixed effect models adjusted for age, gender, time and irritability *versus* time interaction are displayed in table 3 (coefficients for time and irritability-time interaction are available in appendix 1).

Table 3. Irritability predictions on SDQ scores over time in the UK sample

SDQ scores over 3-year follow up	UK sample		
	ADHD	Emotional disorders	No disorder
SDQ emotion overtime	.18(-.004, .37)	.31(.17, .46)***	.29(.25, .33)***
SDQ conduct overtime	.55(.36, .75)***	.46(.35, .58)***	.70(.66, .73)***
SDQ hyperactivity	.11(-.01, .25)	.18(.07, .29)**	.37(.33, .41)***
SDQ impact overtime	.49 (.19, .79)**	.37(.18, .56)***	.22(.19, .26)***
SDQ total overtime	.34(.17, .51)***	.38(.26, .51)***	.53(.49, .57)***

Values correspond to standardized coefficients of linear mixed effect models (with baseline irritability as independent variable and adjusted for age and gender) and their 95% confidence interval in parentheses for SDQ scores over three year follow up.

* $p \leq .05$; ** $p \leq .01$; *** $p \leq .001$

In the absence of a specific disorder, irritability increased SDQ emotion ($p < .001$), conduct ($p < .001$), hyperactivity ($p < .001$), impact ($p < .001$) and total scores ($p < .001$) over 3 years, but a negative interaction between irritability and time was observed for emotion ($p \leq .05$), conduct ($p < .001$), hyperactivity ($p \leq .05$) and total scores ($p < .001$). Thus, although irritability showed a negative impact indexed by higher SDQ scores in healthy kids, the effect was not sustained, and therefore the impact of irritability progressively diminished as the years passed.

In the ADHD group, irritability was associated with increased SDQ conduct ($p < .001$), impact ($p \leq .01$) and total scores ($p < .001$). Interactions between irritability and time were not significant in this group, i.e. the impact of irritability on SDQ scores remained stable over time. In children with emotional disorders, irritability predicted SDQ emotion ($p < .001$), conduct ($p < .001$), hyperactivity ($p \leq .01$), impact ($p < .001$) and total scores over time ($p < .001$). Akin to those with no disorders, the effect of irritability did not sustain, and decreased overtime for SDQ emotion ($p \leq .05$), conduct ($p < .001$),

impact ($p \leq 0.05$) and total scores ($p \leq .01$), indexed by negative interactions between irritability and time. Figure 2 illustrates mixed effect models taking as an example SDQ total scores over time predicted by high (percentile 90) versus low (percentile 10) baseline irritability. SDQ total scores over time are closely related to baseline irritability.

Figure 2. SDQ total scores over three years for high versus low irritability

Longitudinal outcomes in the UK sample

Irritability predictions on clinical outcomes in the UK sample were addressed through DSM-IV diagnoses and indicators of psychosocial impairment at 3-year follow-up. Results are displayed in table 4. Additionally, appendix 2 displays putative results should individuals with ODD be included in the analyses.

DSM-IV diagnoses at follow-up

Logistic regressions were performed, using baseline irritability as independent variable and DSM-IV diagnoses three years later (any disorder; ADHD; emotional disorders; conduct disorder) as dependent variables across groups. Results showed that in healthy children, baseline irritability predicted any disorder ($p < .001$), ADHD ($p < .001$), any emotional disorder ($p < .001$) and conduct disorder ($p < .001$) three years later. For those with ADHD, baseline irritability predicted only conduct disorder ($p \leq .05$) at follow-up, whereas in the emotional disorders group, a trend towards associations was observed for persistence of emotional disorders diagnosis over time. Analyses were repeated including subjects with ODD diagnosis at baseline (see appendix 2). Results showed that in the ADHD + ODD group, irritability predicted any disorder (odds ratio 1.3; 95%CI 1.0, 1.7; $p \leq .01$), persistence of ADHD (odds ratio 1.2; 95% CI 1.0, 1.4; $p \leq .05$), emotional disorder (odds ratio 1.4; 95%CI 1.0, 1.9 $p \leq .05$) and

conduct disorder (odds ratio 1.8; 95% CI 1.3, 2.6; $p < .001$) at follow-up. In the emotional disorders + ODD group, irritability predicted any disorder (odds ratio 1.4; 95% CI 1.2, 1.7; $p < .001$), ADHD (odds ratio 1.6; 95% CI 1.2, 2.3; $p \leq .01$), persistence of emotional disorder (odds ratio 1.2; 95% CI 1.0, 1.4; $p \leq .05$) and conduct disorder (odds ratio 1.6; 95% CI 1.1, 2.3; $p \leq .01$) three years later.

Psychosocial indicators at follow-up across groups

Logistic regressions using baseline irritability as predictor and psychosocial indicators new onset over follow-up (self harm, truancy, police contact, use of mental health services) were performed.

In healthy subjects, baseline irritability predicted onset of self harm ($p < .001$), truancy ($p < .001$), police contact ($p < .001$) and use of mental health services ($p < .001$) over three-year follow-up. In the ADHD group, irritability predicted only self-harm ($p \leq .05$) whereas in the emotional disorders group, irritability predicted only truancy ($p \leq .05$) at follow-up. Analyses were repeated including subjects with ODD and failed to predict any psychosocial indicator three years later in both ADHD and emotional disorders groups.

Table 4. Longitudinal clinical outcomes in the UK sample

DSM-IV diagnoses at 3-year follow-up	UK sample		
	ADHD (n=59)	Emotional disorders (n=121)	No disorder (n=4910)
Any disorder	1.4 (.91, 2.2)	1.2 (.99, 1.6)	1.8 (1.6, 2.0)***
ADHD	1.1 (.80, 1.7)	1.0 (.47, 2.3)	2.1 (1.5, 2.9)***
Emotional disorders	1.0 (.42, 2.7)	1.1 (.86, 1.4)	1.4 (1.1, 1.7)***
Conduct disorder	2.2 (1.1, 4.3)*	.59 (.13, 2.6)	1.9 (1.5, 2.3)***
Psychosocial indicators at 3-year follow-up			
Self harm	1.8 (1.0, 3.3)*	1.0 (.77, 1.4)	1.3 (1.1, 1.6)***
Truancy	2.1 (.95, 4.9)	1.8 (1.0, 3.0)*	1.5 (1.2, 2.0)***
Police contact	1.5 (.90, 2.7)	1.4 (.97, 2.1)	1.4 (1.2, 1.7)***
Mental Health Service	1.1 (.73, 1.9)	.80 (.45, 1.4)	1.5 (1.2, 1.8)***

Values correspond to standardized odds ratio from logistic regression models (with baseline irritability as independent variable and adjusted for age and gender) and their 95% confidence interval in parentheses for clinical outcomes three years later.

* $p \leq .05$; ** $p \leq .01$; *** $p \leq .001$

Discussion

This study provides new empirical evidence on irritability as a dimensional trait that cuts across multiple behavioral and emotional conditions. We used two large and culturally distinct epidemiological samples to examine irritability rates and predictions across diverse clinical settings. Results showed the following: First, irritability is a dimension that varies in intensity across pediatric population; Second, irritability is associated with increased morbidity and impairment across multiple conditions and the additional burden is not explained by ODD or any other diagnoses; Third, irritability is particularly harmful in healthy subjects. Our findings suggest irritability as a prodromal of psychopathology, therefore a potential target for prevention strategies of mental disorders.

In both samples, irritability scores were examined across three distinct groups of children: those with ADHD, emotional disorders and healthy controls. As expected, irritability was lower in controls compared to clinical groups. Irritability rates in children with ADHD and emotional disorders overlapped in both samples, suggesting that irritability underlies externalizing and internalizing behavior similarly.

The stance of irritability in child psychiatry has been a subject of debate, however with practical consequences. The controversy began when irritability was considered part of the youth bipolar disorder (BD) phenotype, leading to a large increase in the diagnostic rate of youth BD (34, 35). Further clinical refinement established that chronic irritability is associated with depression and anxiety, and only the episodic presentation is associated with mania (1, 18, 36-40). Nevertheless, the topic returned to debate following inclusion in the DSM-5 of Disruptive Mood Dysregulation Disorder (DMDD), a new diagnostic category whose main feature is chronic irritability (32). However, DMDD is characterized by high rates of comorbidity and low test-retest reliability (pooled kappa 0.25), and is likely to represent the more severe ends of a continuum rather than a distinct diagnostic category (41)(42, 43). Moreover, parallel to the youth BD and DMDD debates, some argue that irritability should be understood as a core feature of ADHD (44). In contrast to these views considering irritability as a specific feature of specific disorders, our results propose a dimensional view of irritability, cutting across multiple conditions and lacking specificity for any strict diagnosis category.

Cross-sectional analyses in both samples showed that irritability increases morbidity (i.e. SDQ scores) in all groups and longitudinal analyses in the UK sample additionally showed that baseline irritability increases symptomatology 3 years later. Furthermore, coefficients of associations overlapped between children with ADHD and those with emotional disorders both in cross-sectional and longitudinal analyses, suggesting that irritability leads to similar burden across disorders, and its impact does not vary according to the underlying condition. This is the first study to investigate the impact of irritability across multiple clinical settings in large pediatric epidemiological and culturally diverse samples and results seem to converge with preliminary observations in adults, in whom the occurrence of irritability in individuals with major depressive disorder was associated with higher severity and longer duration of symptoms, as well as with poorer impulse control and severe long-term course of illness (45).

Finally, we took advantage of the longitudinal design of the UK sample and showed that, in the long term, irritability was particularly harmful for children without any specific disorder at baseline. In these kids, irritability predicted the onset of some clinical condition 3 years later (any diagnosis, ADHD, any emotional disorder or conduct disorder), and also predicted onset of self-harm, truancy, contact with police and use of mental health services over follow-up. Similar analyses in those with ADHD at baseline showed that irritability predicted conduct disorder and self-harm three years later, whereas in subjects with emotional disorders at baseline, it predicted only truancy over follow-up. These findings suggest that irritability is particularly risky for kids without any disorder. In this respect, it resembles temperamental traits characterized by a tendency to react disproportionately to environmental events with strong emotions of negative valence which, in turn, are strongly associated not only with externalizing behaviors but also with childhood mental disorders in general (46-48). A failure to adequately regulate emotions confers vulnerability to psychopathology and may be central to understanding the overlap between externalizing and internalizing behaviors (49, 50). In fact, the ability to self regulate during childhood is the most important predictor of physical and economic outcomes in adulthood (51).

There are some limitations to this study and its interpretation. First, we based measurement of irritability upon items of ODD. We tried to overcome this limitation by taking a conservative approach and excluding subjects with ODD from the analyses.

Because irritability is intrinsically linked to ODD, we had to ensure that irritability associations were not driven by this diagnosis. Exclusion of ODD children was also needed because ODD is linked to the very outcomes we analyzed, and comorbidity with ADHD and emotional disorders are not negligible. Finally, we could only probe the stance of irritability independently of a diagnosis of ODD. Otherwise, ODD could bias our model. Second, the Brazilian sample is not representative of that country's full ethnic diversity and results may not be generalizable. Furthermore, the Brazilian sample was partly composed by at-risk subjects, which could impact on prevalence rates estimations, although we showed that results were sustained even when restricting analyses to randomly selected children. Finally, because longitudinal analyses were conducted only in the UK sample, the predictive role of irritability in less developed societies remains open.

These limitations notwithstanding, our findings suggest that irritability should be viewed within the RDoC framework, as an underlying dimensional trait adding morbidity across diverse behavioral conditions. Using two large and culturally distinct epidemiological samples we showed that irritability is not explained by any diagnostic category, but is instead an amplifier of current morbidity and a predictor of future burden in the pediatric population (21).

References

1. Stringaris A, Cohen P, Pine DS, Leibenluft E. Adult outcomes of youth irritability: A 20-year prospective community-based study. *Am J Psychiatry*. 2009;166:1048-54.
2. Leibenluft E, Stoddard J. The developmental psychopathology of irritability. *Dev Psychopathol*. 2013;25:1473-87.
3. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, Sanislow C, Wang P. Research domain criteria (rdoc): Toward a new classification framework for research on mental disorders. *Am J Psychiatry*. 2010;167:748-51.
4. Stoddard J, Stringaris A, Brotman MA, Montville D, Pine DS, Leibenluft E. Irritability in child and adolescent anxiety disorders. *Depress Anxiety*. 2014;31:566-73.
5. Drabick DA, Gadow KD. Deconstructing oppositional defiant disorder: Clinic-based evidence for an anger/irritability phenotype. *J Am Acad Child Adolesc Psychiatry*. 2012;51:384-93.

6. Barkley RA. *Adhd and the nature of self-control*. New York: The Guilford Press; 1997.
7. Mandy W, Roughan L, Skuse D. Three dimensions of oppositionality in autism spectrum disorder. *J Abnorm Child Psychol*. 2014;42:291-300.
8. Shaw P, Stringaris A, Nigg J, Leibenluft E. Emotion dysregulation in attention deficit hyperactivity disorder. *Am J Psychiatry*. 2014;171:276-93.
9. Sobanski E, Banaschewski T, Asherson P, Buitelaar J, Chen W, Franke B, Holtmann M, Krumm B, Sergeant J, Sonuga-Barke E, Stringaris A, Taylor E, Anney R, Ebstein RP, Gill M, Miranda A, Mulas F, Oades RD, Roeyers H, Rothenberger A, Steinhausen HC, Faraone SV. Emotional lability in children and adolescents with attention deficit/hyperactivity disorder (adhd): Clinical correlates and familial prevalence. *J Child Psychol Psychiatry*. 2010;51:915-23.
10. Barkley RA, Fischer M. The unique contribution of emotional impulsiveness to impairment in major life activities in hyperactive children as adults. *J Am Acad Child Adolesc Psychiatry*. 2010;49:503-13.
11. Ambrosini PJ, Bennett DS, Elia J. Attention deficit hyperactivity disorder characteristics: Ii. Clinical correlates of irritable mood. *J Affect Disord*. 2013;145:70-6.
12. Comer JS, Pincus DB, Hofmann SG. Generalized anxiety disorder and the proposed associated symptoms criterion change for dsm-5 in a treatment-seeking sample of anxious youth. *Depress Anxiety*. 2012;29:994-1003.
13. Perlis RH, Fava M, Trivedi MH, Alpert J, Luther JF, Wisniewski SR, Rush AJ. Irritability is associated with anxiety and greater severity, but not bipolar spectrum features, in major depressive disorder. *Acta Psychiatr Scand*. 2009;119:282-9.
14. Krebs G, Bolhuis K, Heyman I, Mataix-Cols D, Turner C, Stringaris A. Temper outbursts in paediatric obsessive-compulsive disorder and their association with depressed mood and treatment outcome. *J Child Psychol Psychiatry*. 2013;54:313-22.
15. Stringaris A, Maughan B, Copeland WS, Costello EJ, Angold A. Irritable mood as a symptom of depression in youth: Prevalence, developmental, and clinical correlates in the great smoky mountains study. *J Am Acad Child Adolesc Psychiatry*. 2013;52:831-40.
16. Stringaris A, Goodman R. Longitudinal outcome of youth oppositionality: Irritable, headstrong, and hurtful behaviors have distinctive predictions. *J Am Acad Child Adolesc Psychiatry*. 2009;48:404-12.

17. Burke JD, Hipwell AE, Loeber R. Dimensions of oppositional defiant disorder as predictors of depression and conduct disorder in preadolescent girls. *J Am Acad Child Adolesc Psychiatry*. 2010;49:484-92.
18. Stringaris A, Zavos H, Leibenluft E, Maughan B, Eley TC. Adolescent irritability: Phenotypic associations and genetic links with depressed mood. *Am J Psychiatry*. 2012;169:47-54.
19. Krieger FV, Polanczyk VG, Robert G, Rohde LA, Graeff-Martins AS, Salum G, Gadelha A, Pan P, Stahl D, Stringaris A. Dimensions of oppositionality in a brazilian community sample: Testing the dsm-5 proposal and etiological links. *J Am Acad Child Adolesc Psychiatry*. 2013;52:389-400 e1.
20. Wiggins JL, Mitchell C, Stringaris A, Leibenluft E. Developmental trajectories of irritability and bidirectional associations with maternal depression. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2014;53:1191-205.e4.
21. Casey BJ, Oliveri ME, Insel T. A neurodevelopmental perspective on the research domain criteria (rdoc) framework. *Biol Psychiatry*. 2014;76:350-3.
22. Berkson J. Limitations of the application of fourfold table analysis to hospital data. *Biometrics*. 1946;2:47-53.
23. Green H, Great Britain. Office for National Statistics., Great Britain. Department of Health., Scotland. Scottish Executive. *Mental health of children and young people in great britain, 2004*. Basingstoke ; New York: Palgrave Macmillan; 2005.
24. Parry-Langdon N. Three years on: Survey of the emotional development and well-being of children and young people. . Newport: Office for National Statistics, 2008.
25. Salum GA, Gadelha A, Pan PM, Moriyama TS, Graeff-Martins AS, Tamanaha AC, Alvarenga P, Krieger FV, Fleitlich-Bilyk B, Jackowski A, Sato JR, Brietzke E, Polanczyk GV, Brentani H, Mari JD, Do Rosario MC, Manfro GG, Bressan RA, Mercadante MT, Miguel EC, Rohde LA. High risk cohort study for psychiatric disorders in childhood: Rationale, design, methods and preliminary results. *Int J Methods Psychiatr Res*. 2014.
26. Weissman MM, Wickramaratne P, Adams P, Wolk S, Verdeli H, Olfson M. Brief screening for family psychiatric history: The family history screen. *Arch Gen Psychiatry*. 2000;57:675-82.

27. Goodman R. The strengths and difficulties questionnaire: A research note. *J Child Psychol Psychiatry*. 1997;38:581-6.
28. Stringaris A, Goodman R. The value of measuring impact alongside symptoms in children and adolescents: A longitudinal assessment in a community sample. *J Abnorm Child Psychol*. 2013;41:1109-20.
29. Goodman R. Psychometric properties of the strengths and difficulties questionnaire. *J Am Acad Child Adolesc Psychiatry*. 2001;40:1337-45.
30. Goodman R, Ford T, Richards H, Gatward R, Meltzer H. The development and well-being assessment: Description and initial validation of an integrated assessment of child and adolescent psychopathology. *J Child Psychol Psychiatry*. 2000;41:645-55.
31. Stringaris A, Goodman R. Three dimensions of oppositionality in youth. *J Child Psychol Psychiatry*. 2009;50:216-23.
32. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders 5th ed*. Washington, DC: American Psychiatric Association; 2013.
33. StataCorp. Stata statistical software: Release 10.0. College station, tx: Stata corporation lp. 2007.
34. Biederman J, Klein RG, Pine DS, Klein DF. Resolved: Mania is mistaken for adhd in prepubertal children. *J Am Acad Child Adolesc Psychiatry*. 1998;37:1091-6; discussion 6-9.
35. Moreno C, Laje G, Blanco C, Jiang H, Schmidt AB, Olfson M. National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. *Arch Gen Psychiatry*. 2007;64:1032-9.
36. Leibenluft E, Charney DS, Towbin KE, Bhangoo RK, Pine DS. Defining clinical phenotypes of juvenile mania. *Am J Psychiatry*. 2003;160:430-7.
37. Leibenluft E, Cohen P, Gorrindo T, Brook JS, Pine DS. Chronic versus episodic irritability in youth: A community-based, longitudinal study of clinical and diagnostic associations. *J Child Adolesc Psychopharmacol*. 2006;16:456-66.
38. Leibenluft E. Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. *Am J Psychiatry*. 2011;168:129-42.
39. Stringaris A, Baroni A, Haimm C, Brotman M, Lowe CH, Myers F, Rustgi E, Wheeler W, Kayser R, Towbin K, Leibenluft E. Pediatric bipolar disorder versus severe mood dysregulation: Risk for manic episodes on follow-up. *J Am Acad Child Adolesc Psychiatry*. 2010;49:397-405.

40. Towbin K, Axelson D, Leibenluft E, Birmaher B. Differentiating bipolar disorder-not otherwise specified and severe mood dysregulation. *J Am Acad Child Adolesc Psychiatry*. 2013;52:466-81.
41. Copeland WE, Angold A, Costello EJ, Egger H. Prevalence, comorbidity, and correlates of dsm-5 proposed disruptive mood dysregulation disorder. *Am J Psychiatry*. 2013;170:173-9.
42. Axelson D, Findling RL, Fristad MA, Kowatch RA, Youngstrom EA, Horwitz SM, Arnold LE, Frazier TW, Ryan N, Demeter C, Gill MK, Hauser-Harrington JC, Depew J, Kennedy SM, Gron BA, Rowles BM, Birmaher B. Examining the proposed disruptive mood dysregulation disorder diagnosis in children in the longitudinal assessment of manic symptoms study. *J Clin Psychiatry*. 2012;73:1342-50.
43. Regier DA, Narrow WE, Clarke DE, Kraemer HC, Kuramoto SJ, Kuhl EA, Kupfer DJ. Dsm-5 field trials in the united states and canada, part ii: Test-retest reliability of selected categorical diagnoses. *Am J Psychiatry*. 2013;170:59-70.
44. Skirrow C, McLoughlin G, Kuntsi J, Asherson P. Behavioral, neurocognitive and treatment overlap between attention-deficit/hyperactivity disorder and mood instability. *Expert Rev Neurother*. 2009;9:489-503.
45. Judd LL, Schettler PJ, Coryell W, Akiskal HS, Fiedorowicz JG. Overt irritability/anger in unipolar major depressive episodes: Past and current characteristics and implications for long-term course. *JAMA Psychiatry*. 2013;70:1171-80.
46. Rothbart MK, Ziaie H, O'Boyle CG. Self-regulation and emotion in infancy. In: Eisenberg N, Fabes R A, editors. *Emotion and its regulation in early development: New directions for child development*. San Francisco: Jossey-Bass; 1992. p. 7-23.
47. Rutter M. Temperament, personality and personality disorder. *Br J Psychiatry*. 1987;150:443-58.
48. Thomas A, Chess S. *Temperament and development*. New York: Brunner/Mazel; 1977.
49. Eisenberg N, Cumberland A, Spinrad TL, Fabes RA, Shepard SA, Reiser M, Murphy BC, Losoya SH, Guthrie IK. The relations of regulation and emotionality to children's externalizing and internalizing problem behavior. *Child Dev*. 2001;72:1112-34.
50. Angold A, Costello EJ, Erkanli A. Comorbidity. *J Child Psychol Psychiatry*. 1999;40:57-87.

51. Moffitt TE, Arseneault L, Belsky D, Dickson N, Hancox RJ, Harrington H, Houts R, Poulton R, Roberts BW, Ross S, Sears MR, Thomson WM, Caspi A. A gradient of childhood self-control predicts health, wealth, and public safety. *Proc Natl Acad Sci U S A*. 2011;108:2693-8.

Appendix 1: Results from Linear Mixed Effect Models of irritability on SDQ scores over time (including coefficients for irritability versus time interaction)

SDQ scores over 3-year follow up	UK		
	ADHD	Emotional disorders	No disorder
SDQ emotion overtime			
irr	.18(-.004, .37)	.31(.17, .46)***	.29(.25, .33)***
time	-.03(-.12, .06)	-.17(-.25, -.10)***	.01(.009, .02)***
irr*time	.04(-.01, .09)	-.06(-.11, -.01)*	-.01(-.02, -.001)*
rho	rho .59 (.48, .69)	rho .45(.37, .53)	rho .50 (.49, .51)
SDQ conduct overtime			
irr	.55(.36, .75)***	.46(.35, .58)***	.70(.66, .73)***
time	.05(-.04, .16)	-.01(-.07, .03)	.01(.006, .02)***
irr*time	-.01(-.08, .04)	-.07(-.11, -.03)***	-.06(-.08, -.05)***
rho	rho .53(.41, .64)	rho .43 (.34, .51)	rho .49(.47, .50)
SDQ hyperactivity			
irr	.11(-.01, .25)	.18(.07, .29)**	.37(.33, .41)***
time	-.05(-.13, .01)	-.02(-.07, .01)	.01(.01, .02)***
irr*time	.03(-.01, .07)	-.01(-.04, .01)	-.01(-.02, -.0003)*
rho	rho .42(.30, .54)	rho .63 (.56, .69)	rho .63 (.61, .64)
SDQ impact overtime			
irr	.49 (.19, .79)**	.37(.18, .56)***	.22(.19, .26)***
time	-.09(-.27, .07)	-.26(-.36, -.16)***	.03(.02, .03)***
irr*time	-.01(-.12, .08)	-.08(-.14, -.01)*	-.003(-.01, .008)
rho	rho .35(.22, .49)	rho .43(.34, .52)	rho .31 (.30, .33)
SDQ total overtime			
irr	.34(.17, .51)***	.38(.26, .51)***	.53(.49, .57)***
time	-.03(-.11, .05)	-.09(-.15, -.04)**	.02(.01, .02)***
irr*time	.02(-.02, .07)	-.05(-.09, -.02)**	-.03(-.04, -.02)***
rho	rho .60(.49, .70)	rho .56 (.49, .63)	rho .61 (.60, .62)

Appendix 2.: Results from irritability predictions on clinical outcomes across groups in the UK sample (including subjects with ODD diagnosis)

	ADHD +ODD (n=112)	Emotional disorders +ODD (n=156)	No disorder (n=4910)
DSM-IV diagnoses at 3-year follow-up			
Any disorder	1.3 (1.0, 1.7)**	1.4 (1.2, 1.7)***	1.8 (1.6, 2.0)***
ADHD	1.2 (1.0, 1.4)*	1.6 (1.2, 2.3)**	2.1 (1.5, 2.9)***
Emotional disorders	1.4 (1.0, 1.9)*	1.2 (1.0, 1.4)*	1.4 (1.1, 1.7)***
Conduct disorder	1.8 (1.3, 2.6)***	1.6 (1.1, 2.3)**	1.9 (1.5, 2.3)***
Psychosocial indicators at 3-year follow-up			
Self harm	1.2(.95, 1.7)	1.0(.82, 1.3)	1.3(1.1, 1.6)***
Truancy	1.3(.85, 2.01)	1.4(.91, 2.2)	1.5(1.2, 2.0)***
Police contact	1.0(.79, 1.4)	1.1(.89, 1.5)	1.4(1.2, 1.7)***
Mental Health Service	1.0(.83, 1.4)	1.1(.86, 1.4)	1.5(1.2, 1.8)***

Values correspond to standardized odds ratio from logistic regression models (with baseline irritability as independent variable and adjusted for age and gender) and their 95% confidence interval in parentheses for clinical outcomes three years later.

*p≤ .05; **p≤ .01; ***p≤ .001.

5.3.1 Discussão Artigo 3

A classificação nosológica da irritabilidade segue tópico de controvérsia. Enquanto alguns autores sugerem que a irritabilidade é específica a transtornos como o transtorno de déficit de atenção e hiperatividade (TDAH), outros evidenciam que a irritabilidade deve ser categorizada como “disruptive mood dysregulation disorder (DMDD), ou ainda que a irritabilidade presente em indivíduos com transtornos do espectro autista é distinta das apresentações anteriores. Entretanto, coconceituações contemporâneas sugerem a irritabilidade como um fenótipo dimensional inespecífico que subjaz inúmeros transtornos.

Diante disto, este estudo tem como objetivo investigar o impacto da irritabilidade em diferentes cenários clínicos, examinando se as associações se assemelham ou divergem dependendo do transtorno associado.

Nossos resultados corroboram a hipótese da irritabilidade como um fenótipo dimensional subjacente a múltiplos diagnósticos. Irritabilidade está associada a aumento do prejuízo funcional independentemente do cenário clínico. O impacto atribuído à irritabilidade parece semelhante entre os grupos com TDAH e T. Emocionais.

Entretanto o impacto da irritabilidade mostrou-se particularmente nocivo em indivíduos saudáveis, o que enfatiza a importância do fenótipo no planejamento de intervenções preventivas dos transtornos mentais.

5.4 Artigo 4

**“Polygenic score and environmental risk predict irritability in
children and adolescents”**

Polygenic score and environmental risk predict irritability in children and adolescents

Krieger, F.V.; Polanczyk, G.V.

Irritability, defined as an excessive reactivity to negative emotional stimuli (1), is a frequent and impairing symptom presented by children and adolescents and a component of multiple psychopathological processes. Although irritability is often described as a component of oppositionality, epidemiological and clinical studies show that it is concurrently associated with both internalizing and externalizing behaviors (2) and that it predicts mainly anxiety and major depression in adulthood (3) (4). Because irritability takes part in diverse psychopathological processes across development, understanding its etiology could unveil novel therapeutic interventions and prevention strategies in mental disorders. Behavioral genetics studies suggest that both genetic and environmental factors play a role in determining individual's level of irritability (5, 6). This study investigates genetic influences on the etiology of irritability, through a search of polymorphisms previously implicated in irritability features and the generation of a polygenic score. In addition, we examine how environment affects genetic influence.

Characterized as a dimensional trait, irritability varies from mild annoyance to intense rage and violent verbal or physical aggression towards others or self. It has two distinct components, an affective, often anger, and a behavioral, mostly displayed as aggression. Thus, negative stimuli trigger a negative affect, which is usually followed by aggression (7). In this sense, the construct of irritability resembles temperamental traits characterized by a tendency to high emotionality and negative affect in response to frustration (8-10). This has been variably described in the past as *difficult temperament*, when children had signs of irregularity, negative withdrawal responses to new stimuli, and predominantly negative mood expressions (11), *emotionality*, a designation of psychological instability and proneness to fear, anger and sadness (12), or *neuroticism*, a personality dimension characterized by negative emotionality, anxiety and depression traits, guilty and low self-esteem (13). A more recent model posits that irritability results from a combination of high *negative affectivity*, a tendency to experience negative emotions, and low *effortful control*, which includes inhibitory control and attentional focusing (14). Others have described the same clinical picture as *reactive aggression*, where aggression is impulsive and not premeditated (15, 16). In agreement

to what is described in regard to irritability, all these traits are associated with a broad range of childhood psychopathologies and poor outcomes in adulthood (17-19).

The etiology of irritability includes both genetic and environmental factors. Physical and emotional abuse, low maternal warmth and low familial cohesion have been implicated as environmental risk factors for reactive aggression, anger, impulsive traits and emotional dysregulation (20-22) (23) (24) (25, 26) (27). The heritability of irritability has been estimated at approximately 0.3-0.4 in adolescents and adults (28, 29). Several genes have been implicated in distinct aspects of irritability, among those, the serotonergic, the catecholaminergic and of neurotrophins systems are suggested as particularly relevant (1). The serotonin system is involved in the regulation of emotions and behavior (30). Studies in humans and animal models support that dysfunctions in the serotonergic system are associated with impulsive aggression, poor regulation of emotions and increased risk for depression and anxiety-related traits (31-34). The serotonin transporter linked polymorphic region (5-HTTLPR) is the most studied polymorphism in psychiatry and its short allele (S) have been associated to elevated neuroticism and increased risk for depression (35). 5-HTTLPR S-carriers show elevated amygdala reactivity to threatening stimuli, reactive aggression and a tendency to develop negative emotionality and fear in early childhood (36-39). Apart from 5-HTTLPR, other components are critical to serotonin neurotransmission. Polymorphisms of tryptophan hydroxylase (TPH), responsible for the biosynthesis of serotonin, and of 5-HT_{2A} post-synaptic receptors are strongly related to aggression, impulsivity, poor response inhibition and behavioral control (40) (41) (42). Part of catecholaminergic system, monoamine oxidase (MAO) A and B are enzymes involved in the degradation of neurotransmitters. Several studies have linked MAO A deficiency with impulsivity, aggression, neuroticism and vulnerability to depression (43, 44) (45, 46). Indeed, maltreated children with high levels of MAO A expression were found to be less likely to develop antisocial behavior, despite adversity (47). MAO B activity was found to be associated with impulsiveness and sensation seeking in a sample of male juvenile delinquents (48). Moreover, MAO B polymorphisms are associated with negative emotionality, and susceptibility to depression and anxiety (49). Also part of catecholaminergic system, the catechol-o-methyl transferase (COMT) degrades both dopamine and norepinephrine. COMT polymorphisms influence frontal cortical activation during tasks requiring regulation of attention to threat-related distractors (50).

Also, COMT polymorphisms have been associated with high neuroticism, anxiety-related traits and irritable assault (51) (52). The brain-derived neurotrophic factor (BDNF) influences neuronal differentiation during development, as well as synaptic plasticity (53). BDNF has been implicated in neuroticism and in the pathophysiology of major depression (54, 55) (56).

Despite advances in candidate gene approaches, no single gene is expected to explain complex traits like irritability. A challenge for developmental research following candidate gene approaches is that many polymorphisms are involved in the etiology of a single behavioral trait and individual effect sizes are small. Developmental research requires their aggregation in polygenic scores, where genotypes in many loci are summed (57). Polygenic scores increase power to detect genetic inheritance to quantitative behavioral traits, and this is particularly relevant in the case of irritability where polymorphisms are associated to distinct aspects of the same construct (58, 59).

Following an extensive literature review, we selected 10 polymorphisms belonging to serotonin, MAO, COMT and BDNF, which have been associated to any of the components implicated in irritability. Our primary goal is to investigate the effect of a polygenic score in predicting irritability in a Brazilian community sample of children and adolescents. Additionally, we examine the specificity of the polygenic score to irritability by investigating its effect in predicting emotional symptoms, hyperactivity, conduct problems and DSM-IV disorders associated with irritability. Also, considering the significant effect of environmental stressors in the etiology of irritability, we also examine the effect of polygenic score in the context of environmental risk.

Methods

Sample

Participants are members of the High Risk Cohort Study for the Development of Childhood Psychiatric Disorders, a community study of 2512 children that was carried out in Brazil and has been described in detail elsewhere (60). Briefly, the study included 2512 children, aged 6 to 12 years and was carried out in two cities (Porto Alegre and São Paulo) in southeast Brazil. Sampling procedures included a screening phase in schools, followed by a selection encompassing a randomly selected stratum (n=958) and a high-risk stratum (n=1554) where individuals with a family history of psychopathology and/or ongoing psychiatric symptoms were included. Participants

underwent psychiatric, genetic, neuropsychological and neuroimaging evaluations. The study was approved by the ethics committee of the University of São Paulo (IORG0004884, project IRB registration number: 1132/08).

Of a total of 2512 subjects from the High Risk Cohort Study for the Development of Childhood Psychiatric Disorders, 350 subjects provided complete clinical and genetic data and were included in this report. The difference between the total sample and the one included here occurred because the data collection was carried out through several steps and at different times, particularly genotyping processes. Attrition analysis revealed that those included in this report were younger (mean=9.5, SD 1.9 vs. mean=9.7, SD 1.9; $p = .05$), were more likely to have any diagnosis (30.5% vs. 25.2%; $p = .05$), and a diagnosis of emotional disorder (19.4% vs. 12.3%; $p = .001$) compared to those not included in the analyses. There were no differences in gender, ethnicity, socioeconomic status, ADHD, ODD, CD diagnoses and irritability scores.

Measures

Strengths and Difficulties Questionnaire (SDQ) (61). This is a 25-item questionnaire with robust psychometric properties (62). It comprises five factors, each one with five items: emotional problems, hyperactivity, conduct problems, peer problems, and prosociality. The reliability and validity of SDQ make it a good measure of psychopathology in children and adolescents (63). Although there are also youth and teacher SDQ versions, only the parental version was used here. In this report we use SDQ scores for emotional problems, hyperactivity and conduct problems as continuous dependent variables.

Development and Well-Being Assessment (DAWBA) (64). This is a structured interview administered by lay interviewers who also recorded the verbatim accounts of any reported problems. The questions are closely related to DSM-IV and ICD-10 diagnostic criteria and focus on current problems. The DAWBA makes use of skip rules that allow interviewers to omit many of the detailed questions in a section when the preliminary answer indicates a very low probability of disorder in that domain. In this report, DSM-IV diagnoses and the measurement of irritability were derived from DAWBA.

Environmental factors

Environmental risk was assessed through four variables:

Maternal warmth was derived from Parental Bonding Instrument and assessed maternal bonding and tenderness towards the child. For methodological purposes, scores were inverted and ranged from 0 (always smile and tender) to 5 (never smile or talk to the child) (65).

Physical and emotional abuse was derived from Childhood Trauma Questionnaire and scores ranged from 0 (no, never happened) to 3 (happened or happens frequently) (66).

Family Cohesion was derived from Family Environment Scale and comprised nine items addressing the quality of familial interpersonal relationships. In this report scores were inverted, ranging from 0 (good cohesion) to 9 (poor cohesion). (67).

An environmental risk score was generated by the sum of the four environmental variables (mean= 3.55; 95% CI 3.2, 3.8), and was subsequently stratified on low (below percentile 25), medium (percentile 50) and high-risk (above percentile 75) environment. This allowed testing polygenic associations across distinct categories of environment.

Assessment of irritability

We defined irritability as the irritable dimension of oppositionality. The irritable dimension of oppositionality derives from a cluster of symptoms pertaining to ODD diagnosis and has been extensively described and validated as a reliable measure of irritability in children and adolescents (68) (69) (70) (29, 71). Briefly, those who responded affirmatively to DAWBA's ODD skip question ("*child is more troublesome than others at same age?*") were asked nine questions based on DSM-IV ODD diagnosis items. The irritable dimension was composed by three items: first, "*had temper outbursts?*"; second, "*been touchy and easily annoyed?*"; and third, "*been angry and resentful?*". Response scores were "no more than others" (0), "a little more than others" (1), and "a lot more than others" (2). The three items sum scores composed the irritable dimension, which ranged from 0 ("no more than others" in all three items) to 6 ("a lot more than others" in all three items). Individuals who responded negatively to DAWBA's ODD skip question (n=1238) were considered as scoring zero in all three items. As a continuous variable, the irritable dimension of oppositionality was considered our main outcome.

Genotyping

Saliva DNA Extraction

Saliva samples were collected from a total of 350 subjects using the Oragene DNA Sample Collection Kit (OG-250, DNA Genotek Inc., Ottawa, Ontario, Canada), as recommended by the manufacturer. For the extraction of DNA, 500 μ L of the mixture containing saliva were transferred to an eppendorf tube, which was incubated at 50° C for 1 hour. Then, were added 20 μ L of purifier (DNA Genotek Inc., Ottawa, Ontario, Canada) followed by incubation at 4° C for 15 minutes. After the incubation, the samples were centrifuged at 13,000 rpm for 5min. The supernatant derived from the centrifugation was transferred to a new eppendorf tube and to it added 500 μ L of absolute ethanol. A further incubation was performed in the same manner mentioned above, followed by centrifugation at 13,000 rpm for 3 minutes. The supernatant was discarded and 250 μ L of 70% ethanol added to the pellet formed. After 2 minutes, 70% ethanol was discarded, the pellet stored at room temperature until complete dryness and eluted with 50 μ L of sterile water. The solution was then incubated for 1 hour at 56 ° C and stored at -80° C until use.

Quality assessment

The quantification of samples was performed in Nano Drop ND-2000 Spectrophotometer (Thermo Fisher Scientific, Wilmington, DE, USA). The purity of DNA was determined by the ratio of absorbance and OD260/280 OD260/230, admitting an optimal range from 1.8 to 2.0. The DNA integrity was assessed through electrophoresis in 2% agarose gel.

VNTR analysis

VNTRs analysis in 5-HTTLPR and MAOA were performed with the following primer sequences: 5-HTTLPR forward: 5'- GGCGTTGCCGCTCTGAATGC-3' and reverse: 5'- GAGGGACTGAGCTGGACAACCAC-3'; MAOA forward: 5'- CCAGAACATGAGCACAACG- 3' and reverse: 5'ATTCGGACAGGCTGTAGGAG-3. Amplification was carried out in a final volume of 50 μ L containing 50ng genomic DNA, 200 μ M dNTPs, 10pmol of each primer, 0,5U Taq DNA polymerase (Invitrogen Corporation, Carlsbad, CA, USA), 1X PCR reaction buffer and 1mM MgCl₂. For 5-HTTLPR gene, PCR started with a denaturation at 95° C for 2 min; followed by 35 cycles at 95° C for 30 seconds, 60° C for 1 minute, 72° C for 1 minute and 30 seconds;

and a final extension at 72°C for 10 minutes. For MAO gene, the same process was performed by changing the annealing temperature, that was adjusted to 58°C. PCR products were separated on a 2% agarose gel containing ethidium bromide, and bands were visualized under UV light.

PCR for detection of SNPs

DNA samples were diluted and used at a concentration of 50 ng / μ L. Two and a half microliters of each sample were mixed with two and a half microliters of TaqMan OpenArray Genotyping Master Mix. The samples were then loaded onto the OpenArray plate using the QuantStudio 12K Flex OpenArray AccuFill System (Applied Biosystems, Foster City, CA, USA). After real time qPCR and allelic discrimination, the results were analyzed using TaqMan Genotyper v1.2 software (Applied Biosystems, Foster City, CA, USA).

Polygenic score

Polymorphisms belonging to serotonin, MAO, COMT and BDNF were selected to compose polygenic score if two conditions were satisfied: First, at least two studies supporting an association of that specific polymorphism to at least one of the following aspects of irritability: negative affectivity, impulsive aggression, reactive aggression, negative emotionality, emotional dysregulation, low effortful control, neuroticism, besides depression and anxiety, which are suggested as the most common outcomes. Second, the risk allele for that particular polymorphism has been consistently identified across studies. Because this is the first study to propose a polygenic score for irritability, a conservative approach was taken. Thus, polymorphisms with inconsistent findings and conflicting descriptions regarding risk allele were not included.

A total of 10 polymorphisms were selected within the four genes. Four polymorphisms belonging to serotonin system: 5-HTTLR (22) (31), rs6313 (32) (72), rs6311 (73) (74), rs4570625 (75) (76) and rs11179027 (77) (78). Two polymorphisms linked to MAO A and B activities: MAOA VNTR (79) (43) and rs1799836 (49) (80). One single nucleotide polymorphism (SNP) related to COMT activity: rs165599 (52) (51); and two SNPs pertaining to BDNF: rs7124442 (55) (56) and rs6265 (81) (54). Table 1 displays polymorphisms, along with empirical evidence supporting its selection and description of risk alleles.

Each polymorphism was coded as 0 (homozygous for no-risk allele), 1

(heterozygous) and 2 (homozygous for risk allele). Polygenic score was generated by the sum of 10 individual scores. Because this is the first study to propose a polygenic approach to irritability, no reference data exist to determine the exact contributions of individual polymorphisms to the phenotype. Thus, we used un-weighted counts of risk alleles to construct the score.

Statistical analysis

Data analyses were conducted in three stages: First, we investigated the association between polygenic score and irritability levels through linear regression. We also conducted regression analysis to test the associations between polygenic score and SDQ continuous subscales (symptoms of hyperactivity, conduct and emotional problems). Logistic regressions were performed using polygenic score as predictor and DSM-IV diagnosis often associated to irritability as dependent variables (ADHD, CD, Major depression and ODD). To examine whether the effect of polygenic score was not carried by a single polymorphism, univariate linear regressions were performed using each polymorphism individually as predictor of irritability. Second, we explored the influence of environmental factors on irritability, and examined these factors as confounders of polygenic score findings. Univariate linear regressions were performed testing each environmental factor as predictor of irritability, and those significantly associated were included in a multivariate model. To adjust for potential confounders, a multivariate regression model was carried out including environmental variables and polygenic score as predictors. The third part of statistical analyses included stratified linear regressions where polygenic score predictions on irritability were examine across low, medium and high-risk environments. All analyses were adjusted for age and gender. Standardized coefficients and odds ratios are reported for linear and logistic models respectively. An alpha level of 0.05, two-tailed, was considered significant. Analyses were performed using Stata version 12 (82).

Table 1: Description of polymorphisms selected for polygenic score

Polymorphisms	Gene	MAF	Risk allele	Distribution	Studies supporting association
5-HTTLPR VNTR	HTT	L > S	S allele	LL 35.7% LS 46.4% SS 17.7%	- Neuroticism and anxiety-related traits (31) - Emotional dysregulation (22) - Vulnerability to depression (35) - Emotional impulsivity (37) - Childhood aggression (39)
rs6313	HTR2A	G > A	allele A	GG 33.6% GA 47.8% AA 18.5%	- Impulsivity (32) - Novelty seeking (74)
rs6311	HTR2A	T > C	allele T	CC 17.5% CT 48.9% TT 33.6%	- Anger and aggression (73) - Impulsive traits (83)
rs4570625	TPH2	G > T	allele T	GG 54.1% GT 36.3% TT 9.5%	- Greater neural activity to emotionally arousing pictures (84) - Difficult disengaging attention from fearful facial expressions (75)
rs11179027	TPH2	G > C	allele C	GG 55.1% GC 38.2% CC 6.5%	- Response inhibition (78) - Association with ADHD (77)
MAOA-VNTR	MAO A	2 or 3 repeat= low activity (risk) 34% 3.5 or 4 repeat= high activity 51.7% Heterozygous (only females) 14.2%			- Trait aggression (85) - Aggressiveness, impulsiveness (86)
rs1799836	MAO B	C > T	allele T	CC 41.8% CT 22.6% TT 35.5%	- Attention impulsiveness, higher stress reaction (80) - Negative emotionality (49)
rs165599	COMT	A > G	allele G	AA 33% AG 45.3% GG 21.5%	- Higher irritable assault (52) - Anxiety related traits, neuroticism (51)
rs7124442	BDNF	C > T	allele T	CC 59.2% CT 26.5% TT 14.2%	- Internalizing symptoms (55) - Major depression (56)
rs6265	BDNF	C > T	allele T	CC 80.6% CT 16.6% TT 2.7%	- Neuroticism (54) - Major depression (81)

HTT=serotonin transporter; HTR2A= serotonin receptor 2A; TPH2= tryptophan hydroxylase 2; MAO A= monoamine oxidase A; MAO B= monoamine oxidase B; COMT= catechol-o-methyl transferase; BDNF= brain derived neurotrophic factor; VNTR= variable number tandem repeat; MAF= minor allele frequency.

Results

Our sample included 350 subjects with mean age of 9.5 years (SD 1.9), and a similar proportion between males (53%) and females. The sample was composed predominantly by caucasians (65.5%), and 77% of them belong to middle-class families. Approximately one third (n=107) had a DSM-IV diagnosis. A diagnosis of emotional disorders was found in 19% of the sample, followed by ADHD (11%). The mean score for irritability was 1.06 (SD 1.6). Table 2 displays sample characteristics.

Table 2. Sample characteristics

Sample	N=350
Age , years (SD)	9.5 (1.9)
Gender male , n (%)	186 (53.1)
Ethnicity caucasian , n (%)	228 (65.5)
IQ , mean (95% CI)	101 (99, 103)
Socioeconomic status	
Low/very low , n (%)	43 (12.2)
Medium , n (%)	271 (77.4)
High , n (%)	36 (10.2)
SDQ scores	
Emotional problems (0-10), mean (95% CI)	4.6 (4.3, 4.9)
Conduct problems (0-10), mean (95% CI)	3.1 (2.9, 3.4)
Hyperactivity symptoms (0-10), mean (95% CI)	5.2 (4.8, 5.5)
Impact scores (0-10), mean (95% CI)	1.1 (.94, 1.3)
Total scores (0-40), mean (95% CI)	15.8 (14.9, 16.6)
DSM-IV diagnoses	
Any diagnosis , n (%)	107 (30.5)
Emotional disorders , n (%)	68 (19.4)
ADHD , n (%)	40 (11.4)
ODD , n (%)	23 (6.5)
CD , n (%)	5 (1.4)
Irritability (0-6), mean (95% CI)	1.06 (.89, 1.2)
Polygenic score (2-16), mean (95% CI)	7.3 (7.0, 7.5)
Environmental score (0-15), mean (95% CI)	3.5 (3.2, 3.8)

Polygenic Score and irritability

The polygenic score was found to significantly predict irritability. The correlation between irritability and polygenic score was $r = .13$ ($p = .05$). Results from linear regression showed a significant association between polygenic score and irritability (coef. = .07; 95% CI .01, .12; $p = .01$; $r^2 = .019$). Figure 1 displays fitted regression of polygenic score on irritability.

Figure 1: Fitted regression of polygenic score on irritability

To investigate if the association between polygenic score and irritability was driven by a single polymorphism, univariate regression analyses were performed for each polymorphism as independent variable. Results are displayed in table 3. No one single polymorphism showed a significant association with irritability, although a trend towards association was observed for 5-HTTLPR and rs4570625.

Table 3: Univariate analyses for each polymorphism

Polymorphisms	Coefficient (95% CI)	P > t
5-HTTPLR VNTR	.18 (-.001, .37)	.052
rs6313	-.01 (-.20, .17)	.86
rs6311	.01 (-.17, .21)	.84
rs4570625	.19 (-.005, .40)	.056
rs11179027	.10 (-.10, .32)	.33
MAO A VNTR	-.01 (-.16, .13)	.84
rs1799836	.10 (-.05, .25)	.19
rs165599	.009 (-.17, .19)	.91
rs7124442	.14 (-.03, .32)	.12
rs6265	.18 (-.10, .47)	.20

Analyses were adjusted for age and gender.

Polygenic Score and other symptoms and disorders

The polygenic score was found not to predict hyperactivity, conduct and emotional problems. Again, polygenic score did not predict SDQ emotional symptoms (coef.= .04; 95% CI -.002, .08; p= .06); SDQ hyperactivity (coef.= .03; 95% CI -.01, .07; p= .16); SDQ conduct problems (coef.= .01; 95% CI -.02, .06; p= .43); and SDQ total score (coef.= .03; 95% CI -.005, .08; p= .08).

In addition, we explored associations between polygenic score and DSM-IV diagnoses (emotional disorders, ADHD, ODD and CD). Polygenic score failed to

predict emotional disorders (odds ratio= 1.1; 95% CI .98, 1.2; $p = .07$); major depression (odds ratio=1.0; 95% CI .88, 1.3; $p = .43$); ADHD (odds ratio= 1.0; 95% CI .93, 1.2; $p = .28$); ODD (odds ratio= 1.0; 95% CI .91, 1.3; $p = .31$); and CD (odds ratio= 1.3; 95% CI .94, 1.8; $p = .10$).

Polygenic score and environmental risk

Our second aim was to explore whether environmental factors involved in the pathogenesis of irritability influence polygenic score predictions. Low maternal warmth (coef.= .38; 95% CI .22, .54; $r^2 .06$; $p < .001$), low family cohesion (coef.= .23; 95% CI .17, .30; $r^2 .12$; $p < .001$), physical abuse (coef.= .78; 95% CI .54, 1.0; $r^2 .10$; $p < .001$) and emotional abuse (coef.= .35; 95% CI .23, .48; $r^2 .08$; $p < .001$) were all significantly associated to irritability.

An environmental risk score was generated by the sum of the four following variables: low maternal warmth, low family cohesion, physical abuse and emotional abuse. As expected, environmental risk score was highly associated to irritability (coef.= .20; 95% CI .16, .24; $p < .001$; $r^2 .21$). Correlation between polygenic and environment risk scores was $r = .034$, and was not significant ($p = .51$). Even after taking into account environmental factors, polygenic score remained significantly associated to irritability (coef.= .06; 95% CI .01, .11; $p \leq .01$). The full model explained approximately a fourth of irritability variability ($r^2 = .23$). Eventually, an interaction between polygenic score and risk environment was included in the model, but was not significant (coef.=.01; 95% CI -.003, .02; $p = .12$).

Finally, we examined the effect of polygenic score on irritability across distinct categories of environmental risk: low (below percentile 25), medium (percentile 50) and high-risk (above percentile 75) environments. Results from stratified linear regressions suggest that polygenic influence on irritability is stronger in high-risk environment (table 4). Of note, correlation between polygenic score and low-risk environment was $r = -.04$ ($p = .55$), whereas with high-risk correlation increased to $r = .16$ ($p = .05$). Figure 2 illustrates associations between polygenic score and irritability across low, medium and high-risk environments.

Table 4. Polygenic score predictions across environmental risk

Environment	Polygenic score predictions on irritability	r^2
Low risk (n=153)	.03 (-.02, .09)	.01
Medium risk (n=58)	.05 (-.05, .16)	.03
High risk (n=139)	.11 (.01, .22)*	.04

Values correspond to standardized coefficients of association, and their 95% confidence interval.

Analyses were adjusted for age and gender. * $p < .05$

Figure 2: Linear predictions of polygenic score on irritability across environmental risk categories

Discussion

This study provides novel empirical evidence on genetic influence on the etiology of irritability. In particular, results show the following: first, polygenic predicted irritability in individuals aging 6 to 12 years from a Brazilian community sample; second, the effect of the polygenic score is specific to irritability; third, polygenic influence remained significant even after taking into account environmental factors also related to the etiology of irritability; and third, genetic influence on irritability appears to be stronger in high-risk environments.

The first aim of this article was to investigate genetic influence on the etiology of irritability through a polygenic score. We found a significant association between polygenic score and irritability in children and adolescents. To our knowledge, this is the first study to take this approach in regard to irritability. Polygenic scores studies often select polymorphisms that have been previously reported in genome-wide association studies (GWAS) for that particular disorder or trait (57) (87-89). The lack of GWAS investigating irritability and the different approaches used to define irritability across studies required a careful literature review. Temperamental traits characterized by negative affect, emotionality, anger, reactive aggression, attentional bias towards threat, low effortful control and longitudinal outcomes of irritability including depression and anxiety were considered in our search. Therefore, we ended up selecting polymorphisms related to multiple behaviors and neurobiological processes that are component of irritability. What is particular interesting about our findings is that despite several systems involved, polygenic score predicted irritability specifically and failed to predict major depression, ADHD, CD and ODD. Moreover, polygenic score did not predict continuous measures of emotional, hyperactivity and conduct symptoms. A potential explanation for such specificity is that a polygenic score encompassing a broad range of mechanisms would be able to predict only precursors of psychopathology or undifferentiated phenotypes, for instance irritability. Studies linking low self and emotional regulation to innumerable poor outcomes support the hypothesis of irritability as a precursor of psychopathology (90) (91) (92).

The second aim of this report explored potential environmental confounders of genetic influence on the etiology of irritability. Surprisingly, polygenic score remained a significant predictor of irritability even after adjusting for environmental variables strongly related to the phenotype. Furthermore, a multivariate model including

environmental factors and polygenic score as predictors explained a fourth of irritability variability. These findings suggest an additional effect between genes and environment. However, when environment was stratified, polygenic influence on irritability showed to be stronger in the high-risk environment. Indeed, Feinberg et al. showed that genetic influences increase in high-risk environments (93). Nevertheless, we found a significant increase in the correlations between polygenic score and high-risk environment compared to low-risk. This finding suggests a gene-environment correlation (r_{GE}), the process by which an individual's genotype influences or is associated with exposure environment. The reason why r_{GE} matters is that it can inform how psychopathology develops overtime, which is particularly important in the case of irritability (94).

Our study should be seen in the light of limitations. First, our sample was not representative of the full ethnic diversity of the Brazilian population, so generalizations should be cautious. Second, our measure of irritability is derived from items pertaining to ODD diagnosis. Unfortunately, despite the crucial role of irritability in psychopathology, standardized measures of it are still needed. Third, environmental measures were assessed retrospectively and are therefore liable to recall bias. Finally, at this time point, our data are cross-sectional, limiting the strength of causal inferences.

Our results have some implications particularly regarding the mechanisms by which irritability leads to diverse psychopathological trajectories. On the one hand, we were able to identify genetic influence on the etiology of irritability. On the other hand, we examined environmental factors implicated on the phenotype. The evidence of r_{GE} suggests that bidirectional relations between gene and environment may determine irritability gradients and their persistence across development. Therefore, our results enlighten potential mechanisms underlying psychopathological processes, especially the origins of a dimensional phenotype that takes part in a wide range of disorders.

In sum this study provides empirical evidence to improve the understanding of irritability etiology. Our results showed a direct effect of polygenic score on the etiology of irritability that was above and beyond environmental confounders. Also a direct association of environmental risk was found and the interplay between gene and environment is suggested to comprise r_{GE} . As the first study to take this approach regarding irritability, clearly, our results need replication in diverse samples.

References

1. Leibenluft E, Stoddard J. The developmental psychopathology of irritability. *Dev Psychopathol.* 2013;25:1473-87.
2. Whelan YM, Stringaris A, Maughan B, Barker ED. Developmental continuity of oppositional defiant disorder subdimensions at ages 8, 10, and 13 years and their distinct psychiatric outcomes at age 16 years. *J Am Acad Child Adolesc Psychiatry.* 2013;52:961-9.
3. Stringaris A, Cohen P, Pine DS, Leibenluft E. Adult outcomes of youth irritability: A 20-year prospective community-based study. *Am J Psychiatry.* 2009;166:1048-54.
4. Brotman MA, Schmajuk M, Rich BA, Dickstein DP, Guyer AE, Costello EJ, Egger HL, Angold A, Pine DS, Leibenluft E. Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. *Biol Psychiatry.* 2006;60:991-7.
5. Saudino KJ. Behavioral genetics and child temperament. *J Dev Behav Pediatr.* 2005;26:214-23.
6. Goldsmith HH, Buss KA, Lemery KS. Toddler and childhood temperament: Expanded content, stronger genetic evidence, new evidence for the importance of environment. *Dev Psychol.* 1997;33:891-905.
7. Berkowitz L. Frustration-aggression hypothesis: Examination and reformulation. *Psychol Bull.* 1989;106:59-73.
8. Caprara GV, Cinanni V, D'Imperio G, Passerini S. Indicators of impulsive aggression: Present status of research on irritability and emotional susceptibility scales. *Personality and Individual Differences.* 1985;6:665-74.
9. Shiner R, Caspi A. Personality differences in childhood and adolescence: Measurement, development, and consequences. *J Child Psychol Psychiatry.* 2003;44:2-32.
10. Zentner M, Shiner RL. *Handbook of temperament.* New York: Guilford Press; 2012.
11. Chess S, Thomas A. *Temperament: Theory and practice.* New York: World Books; 1966.

12. Buss AH, Plomin R. *Temperament: Early developing personality traits*. Hillsdale, NJ: Erlbaum; 1984.
13. Digman JM. Personality structure: Emergence of the five-factor model. *Annu Rev Psychol*. 1990;41:417-40.
14. Rothbart MK, Ahadi SA. Temperament and the development of personality. *J Abnorm Psychol*. 1994;103:55-66.
15. Vitiello B, Stoff DM. Subtypes of aggression and their relevance to child psychiatry. *J Am Acad Child Adolesc Psychiatry*. 1997;36:307-15.
16. Frick PJ, Morris AS. Temperament and developmental pathways to conduct problems. *J Clin Child Adolesc Psychol*. 2004;33:54-68.
17. Eisenberg N, Cumberland A, Spinrad TL, Fabes RA, Shepard SA, Reiser M, Murphy BC, Losoya SH, Guthrie IK. The relations of regulation and emotionality to children's externalizing and internalizing problem behavior. *Child Dev*. 2001;72:1112-34.
18. Lengua LJ, West SG, Sandler IN. Temperament as a predictor of symptomatology in children: Addressing contamination of measures. *Child Dev*. 1998;69:164-81.
19. Caspi A, Henry B, McGee RO, Moffitt TE, Silva PA. Temperamental origins of child and adolescent behavior problems: From age three to age fifteen. *Child Dev*. 1995;66:55-68.
20. Springer KW, Sheridan J, Kuo D, Carnes M. Long-term physical and mental health consequences of childhood physical abuse: Results from a large population-based sample of men and women. *Child Abuse and Neglect*. 2007;31:517-30.
21. Kochanska G, Kim S. Difficult temperament moderates links between maternal responsiveness and children's compliance and behavior problems in low-income families. *J Child Psychol Psychiatry*. 2013;54:323-32.
22. Kochanska G, Philibert RA, Barry RA. Interplay of genes and early mother-child relationship in the development of self-regulation from toddler to preschool age. *J Child Psychol Psychiatry*. 2009;50:1331-8.
23. Dumas JE, Nissley J, Nordstrom A, Smith EP, Prinz RJ, Levine DW. Home chaos: Sociodemographic, parenting, interactional, and child correlates. *J Clin Child Adolesc Psychol*. 2005;34:93-104.

24. Lemery-Chalfant K, Kao K, Swann G, Goldsmith HH. Childhood temperament: Passive gene-environment correlation, gene-environment interaction, and the hidden importance of the family environment. *Dev Psychopathol.* 2013;25:51-63.
25. Owens EB, Shaw DS, Vondra JI. Relations between infant irritability and maternal responsiveness in low-income families. *Infant Behav Dev.* 1998;21:761-77.
26. Shields A, Cicchetti D. Reactive aggression among maltreated children: The contributions of attention and emotion dysregulation. *J Clin Child Psychol.* 1998;27:381-95.
27. Dodge KA, Bates JE, Pettit GS. Mechanisms in the cycle of violence. *Science.* 1990;250:1678-83.
28. Coccaro EF, Bergeman CS, Kavoussi RJ, Seroczynski AD. Heritability of aggression and irritability: A twin study of the buss-durkee aggression scales in adult male subjects. *BPS.* 1997;41:273-84.
29. Stringaris A, Zavos H, Leibenluft E, Maughan B, Eley TC. Adolescent irritability: Phenotypic associations and genetic links with depressed mood. *Am J Psychiatry.* 2012;169:47-54.
30. Popova NK. From gene to aggressive behavior: The role of brain serotonin. *Neurosci Behav Physi.* 2008; 38:471-75.
31. Lesch K-P, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, Benjamin J, Müller CR, Hamer DH, Murphy DL. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science.* 1996;274:1527-31.
32. Stoltenberg SF, Christ CC, Highland KB. Serotonin system gene polymorphisms are associated with impulsivity in a context dependent manner. *Prog. Neuropsychopharmacol. Biol. Psychiatry.* 2012;39:182-91.
33. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R. Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science.* 2003;301:386-9.
34. Spinelli S, Schwandt ML, Lindell SG, Newman TK, Heilig M, Suomi SJ, Higley JD, Goldman D, Barr CS. Association between the recombinant human serotonin transporter linked promoter region polymorphism and behavior in rhesus macaques during a separation paradigm. *Dev Psychopathol.* 2007;19:977-87.

35. Caspi A, Hariri AR, Holmes A, Uher R, Moffitt TE. Genetic sensitivity to the environment: The case of the serotonin transporter gene and its implications for studying complex diseases and traits. *Am J Psychiatry*. 2010;167:509-27.
36. Hariri AR, Mattay VS, Tessitore A, Kolachana B, Fera F. Serotonin transporter genetic variation and the response of the human amygdala. *Science*. 2002; 297:400-03.
37. Carver CS, Johnson SL, Joormann J, Kim Y, Nam JY. Serotonin transporter polymorphism interacts with childhood adversity to predict aspects of impulsivity. *Psychol Sci*. 2011;22:589-95.
38. Pauli-Pott U, Friedel S, Friedl S, Hinney A, Hebebrand J. Serotonin transporter gene polymorphism (5-HTTLPR), environmental conditions, and developing negative emotionality and fear in early childhood. *J Neural Transm*. 2009;116:503-12.
39. Beitchman JH, Baldassarra L, Mik H, De Luca V, King N, Bender D, Ehteshami S, Kennedy JL. Serotonin transporter polymorphisms and persistent, pervasive childhood aggression. *Am J Psychiatry*. 2006;163:1103-5.
40. Stoltenberg SF, Glass JM, Chermack ST, Flynn HA, Li S, Weston ME, Burmeister M. Possible association between response inhibition and a variant in the brain-expressed tryptophan hydroxylase-2 gene. *Psychiatr Genet*. 2006;16:35-8.
41. Perez-Rodriguez MM, Weinstein S, New AS, Bevilacqua L, Yuan Q, Zhou Z, Hodgkinson C, Goodman M, Koenigsberg HW, Goldman D, Siever LJ. Tryptophan-hydroxylase 2 haplotype association with borderline personality disorder and aggression in a sample of patients with personality disorders and healthy controls. *J Psychiatr Res*. 2010;44:1075-81.
42. Bjork JM, Moeller FG, Dougherty DM, Swann AC, Machado MA, Hanis CL. Serotonin 2a receptor t102c polymorphism and impaired impulse control. *Am. J. Med. Genet*. 2002;114:336-9.
43. Meyer-Lindenberg A, Buckholtz JW, Kolachana B, Hariri AR, Pezawas L, Blasi G, Wabnitz A, Honea R, Verchinski B, Callicott JH, Egan M, Mattay V, Weinberger DR. Neural mechanisms of genetic risk for impulsivity and violence in humans. *Proc. Natl. Acad. Sci. U.S.A.* 2006;103:6269-74.
44. Brunner HG, Nelen M, Breakefield XO, Ropers HH, van Oost BA. Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase a. *Science*. 1993;262:578-80.

45. Eley TC, Tahir E, Angleitner A, Harriss K, McClay J, Plomin R, Riemann R, Spinath F, Craig I. Association analysis of maoa and comt with neuroticism assessed by peers. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 2003;120B:90-6.
46. Rivera M, Gutierrez B, Molina E, Torres-Gonzalez F, Bellon JA, Moreno-Kustner B, King M, Nazareth I, Martinez-Gonzalez LJ, Martinez-Espin E, Munoz-Garcia MM, Motrico E, Martinez-Canavate T, Lorente JA, Luna JD, Cervilla JA. High-activity variants of the umaoa polymorphism increase the risk for depression in a large primary care sample. *Am J Med Genet B Neuropsychiatr Genet.* 2009;150B:395-402.
47. Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, Taylor A, Poulton R. Role of genotype in the cycle of violence in maltreated children. *Science.* 2002;297:851-4.
48. Ruchkin VV, Koposov RA, af Klinteberg B, Orelund L, Grigorenko EL. Platelet mao-b, personality, and psychopathology. *J Abnorm Psychol.* 2005;114:477-82.
49. Dlugos AM, Palmer AA, de Wit H. Negative emotionality: Monoamine oxidase b gene variants modulate personality traits in healthy humans. *J Neural Transm.* 2009;116:1323-34.
50. Bishop SJ, Cohen JD, Fossella J, Casey BJ, Farah MJ. Comt genotype influences prefrontal response to emotional distraction. *Cognitive, Affective, & Behavioral Neuroscience.* 2006;6:62-70.
51. Stein MB, Fallin MD, Schork NJ, Gelernter J. Comt polymorphisms and anxiety-related personality traits. *Neuropsychopharmacology.* 2005;30:2092-102.
52. Flory JD, Xu K, New AS, Finch T, Goldman D, Siever LJ. Irritable assault and variation in the comt gene. *Psychiatr Genet.* 2007;17:344-6.
53. Thoenen H. Neurotrophins and neuronal plasticity. *Science.* 1995;270:593-8.
54. Sen S, Nesse RM, Stoltenberg SF, Li S, Gleiberman L, Chakravarti A, Weder AB, Burmeister M. A bdnf coding variant is associated with the neo personality inventory domain neuroticism, a risk factor for depression. *Neuropsychopharmacology.* 2002;28:397-401.
55. O'Donnell KJ, Glover V, Holbrook JD, O'Connor TG. Maternal prenatal anxiety and child brain-derived neurotrophic factor (bdnf) genotype: Effects on internalizing symptoms from 4 to 15 years of age. *Dev Psychopathol.* 2014;26:1255-66.

56. Verhagen M, van der Meij A, van Deurzen PAM, Janzing JGE, Vasquez AA, a, Buitelaar JK, Franke B. Meta-analysis of the bdnf val66met polymorphism in major depressive disorder: Effects of gender and ethnicity. *Mol Psychiatry*. 2008;15:260-71.
57. Plomin R. Commentary: Missing heritability, polygenic scores, and gene-environment correlation. *J Child Psychol Psychiatry*. 2013;54:1147-9.
58. Plomin R, Haworth CMA, Davis OSP. Common disorders are quantitative traits. *Nat. Rev. Genet*. 2009;10:872-8.
59. Rucker JJH, McGuffin P. Polygenic heterogeneity: A complex model of genetic inheritance in psychiatric disorders. *Biol Psychiatry*. 2010;68:312-3.
60. Salum GA, Gadelha A, Pan PM, Moriyama TS, Graeff-Martins AS, Tamanaha AC, Alvarenga P, Krieger FV, Fleitlich-Bilyk B, Jackowski A, Sato JR, Brietzke E, Polanczyk GV, Brentani H, Mari JdJ, Do Rosário MC, Manfro GG, Bressan RA, Mercadante MT, Miguel EC, Rohde LA. High risk cohort study for psychiatric disorders in childhood: Rationale, design, methods and preliminary results. *Int J Methods Psychiatr Res*. 2014.
61. Goodman R. The strengths and difficulties questionnaire: A research note. *J Child Psychol Psychiatry*. 1997;38:581-6.
62. Goodman R. Psychometric properties of the strengths and difficulties questionnaire. *J Am Acad Child Adolesc Psychiatry*. 2001;40:1337-45.
63. Goodman R, Ford T, Simmons H, Gatward R, Meltzer H. Using the strengths and difficulties questionnaire (sdq) to screen for child psychiatric disorders in a community sample. *Br J Psychiatry*. 2000;177:534-9.
64. Goodman R, Ford T, Richards H, Gatward R, Meltzer H. The development and well-being assessment: Description and initial validation of an integrated assessment of child and adolescent psychopathology. *J Child Psychol Psychiatry*. 2000;41:645-55.
65. Parker G. The parental bonding instrument. A decade of research. *Soc Psychiatry Psychiatr Epidemiol*. 1990;25:281-2.
66. Bernstein DP, Ahluvalia T, Pogge D, Handelsman L. Validity of the childhood trauma questionnaire in an adolescent psychiatric population. *J Am Acad Child Adolesc Psychiatry*. 1997;36:340-8.
67. Moos RH. Conceptual and empirical approaches to developing family-based assessment procedures: Resolving the case of the family environment scale. *Family Process*. 1990;29:199-208- discussion 9-11.

68. Stringaris A, Goodman R. Three dimensions of oppositionality in youth. *J Child Psychol Psychiatry*. 2009;50:216-23.
69. Stringaris A, Goodman R. Longitudinal outcome of youth oppositionality: Irritable, headstrong, and hurtful behaviors have distinctive predictions. *J Am Acad Child Adolesc Psychiatry*. 2009;48:404-12.
70. Ezpeleta L, Granero R, de la Osa N, Penelo E, Domenech JM. Dimensions of oppositional defiant disorder in 3-year-old preschoolers. *J Child Psychol Psychiatry*. 2012.
71. Burke JD, Hipwell AE, Loeber R. Dimensions of oppositional defiant disorder as predictors of depression and conduct disorder in preadolescent girls. *J Am Acad Child Adolesc Psychiatry*. 2010;49:484-92.
72. Ben-Efraim YJ, Wasserman D, Wasserman J, Sokolowski M. Family-based study of htr2a in suicide attempts: Observed gene, gene $\times$ environment and parent-of-origin associations. *Mol Psychiatry*. 2013;18:758-66.
73. Giegling I, Hartmann AM, Möller H-J, Rujescu D. Anger- and aggression-related traits are associated with polymorphisms in the 5-HT-2a gene. *J Affect Disord*. 2006;96:75-81.
74. Serretti A, Calati R, Giegling I, Hartmann AM, Möller H-J, Colombo C, Rujescu D. 5-HT2a snps and the temperament and character inventory. *Prog. Neuropsychopharmacol. Biol. Psychiatry*. 2007;31:1275-81.
75. Forssman L, Peltola MJ, Yrttiaho S, Puura K, Mononen N, Lehtimäki T, Leppänen JM. Regulatory variant of the tph2 gene and early life stress are associated with heightened attention to social signals of fear in infants. *J Child Psychol Psychiatry*. 2014;55:793-801.
76. Brown SM, Peet E, Manuck SB, Williamson DE, Dahl RE, Ferrell RE, Hariri AR. A regulatory variant of the human tryptophan hydroxylase-2 gene biases amygdala reactivity. *Mol Psychiatry*. 2005;10:805-.
77. Walitza S, Renner TJ, Dempfle A, Konrad K, Wewetzer C, Halbach A, Herpertz-Dahlmann B, Remschmidt H, Smidt J, Linder M, Flierl L, Knölker U, Friedel S, Schäfer H, Gross C, Hebebrand J, Warnke A, Lesch KP. Transmission disequilibrium of polymorphic variants in the tryptophan hydroxylase-2 gene in attention-deficit/hyperactivity disorder. *Mol Psychiatry*. 2005;10:1126-32.

78. Baehne CG, Ehli AC, Plichta MM, Conzelmann A. Tph2 gene variants modulate response control processes in adult adhd patients and healthy individuals. *Mol Psychiatry*. 2008;14:1032-9.
79. Beitchman JH, Mik HM, Ehtesham S, Douglas L, Kennedy JL. Maa and persistent, pervasive childhood aggression. *Mol Psychiatry*. 2004;9:546-7.
80. Li J, Wang Y, Hu S, Zhou R, Yu X, Wang B, Guan L, Yang L, Zhang F, Faraone SV. The monoamine oxidase b gene exhibits significant association to adhd. *Am. J. Med. Genet. B Neuropsychiatr. Genet*. 2008;147:370-4.
81. Schumacher J, Jamra RA, Becker T, Ohlraun S, Klopp N, Binder EB, Schulze TG, Deschner M, Schmal C, Höfels S, Zobel A, Illig T, Propping P, Holsboer F, Rietschel M, Nöthen MM, Cichon S. Evidence for a relationship between genetic variants at the brain-derived neurotrophic factor (bdnf) locus and major depression. *Biol Psychiatry*. 2005;58:307-14.
82. StataCorp. Stata statistical software: Release 10.0. College station, tx: Stata corporation lp. 2007.
83. Preuss UW, Koller G, Bondy B, Bahlmann M, Soyka M. Impulsive traits and 5-ht2a receptor promoter polymorphism in alcohol dependents: Possible association but no influence of personality disorders. *Neuropsychobiology*. 2001;43:186-91.
84. Herrmann MJ, Huter T, Müller F, Mühlberger A, Pauli P, Reif A, Renner T, Canli T, Fallgatter AJ, Lesch K-P. Additive effects of serotonin transporter and tryptophan hydroxylase-2 gene variation on emotional processing. *Cereb. Cortex*. 2007;17:1160-3.
85. Alia-Klein N, Goldstein RZ, Kriplani A, Logan J, Tomasi D, Williams B, Telang F, Shumay E, Biegon A, Craig IW, Henn F, Wang G-J, Volkow ND, Fowler JS. Brain monoamine oxidase a activity predicts trait aggression. *J. Neurosci*. 2008;28:5099-104.
86. Manuck SB, Flory JD, Ferrell RE, Mann JJ, Muldoon MF. A regulatory polymorphism of the monoamine oxidase-a gene may be associated with variability in aggression, impulsivity, and central nervous system serotonergic responsivity. *Psychiatry Res*. 2000;95:9-23.
87. Belsky DW, Moffitt TE, Baker TB, Biddle AK, Evans JP, Harrington H, Houts R, Meier M, Sugden K, Williams B, Poulton R, Caspi A. Polygenic risk and the

developmental progression to heavy, persistent smoking and nicotine dependence: Evidence from a 4-decade longitudinal study. *JAMA Psychiatry*. 2013;70:534-42.

88. Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, Sklar P, Purcell Leader SM, Stone JL, Sullivan PF, Ruderfer DM, McQuillin A, Morris DW, O'Dushlaine CT, Corvin A, Holmans PA, et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*. 2009;460:748-52.

89. Stergiakouli E, Martin J, Hamshere ML, Langley K, Evans DM, St Pourcain B, Timpson NJ, Owen MJ, O'Donovan M, Thapar A, Davey Smith G. Shared genetic influences between attention-deficit/hyperactivity disorder (adhd) traits in children and clinical adhd. *J Am Acad Child Adolesc Psychiatry*. 2015. DOI: <http://dx.doi.org/10.1016/j.jaac.2015.01.010> (in press).

90. Kring AM, Sloan DM. *Emotion regulation and psychopathology: A transdiagnostic approach to etiology and treatment*. New York: The Guilford Press; 2010.

91. Moffitt TE, Arseneault L, Belsky D, Dickson N, Hancox RJ, Harrington H, Houts R, Poulton R, Roberts BW, Ross S, Sears MR, Thomson WM, Caspi A. A gradient of childhood self-control predicts health, wealth, and public safety. *Proc Natl Acad Sci U S A*. 2011;108:2693-8.

92. Gjone H, Stevenson J. A longitudinal twin study of temperament and behavior problems: Common genetic or environmental influences? *J Am Acad Child Adolesc Psychiatry*. 1997;36:1448-56.

93. Feinberg ME, Button TMM, Neiderhiser JM, Reiss D, Hetherington EM. Parenting and adolescent antisocial behavior and depression: Evidence of genotype x parenting environment interaction. *Arch Gen Psychiatry*. 2007;64:457-65.

94. Knafo A, Jaffee SR. Gene-environment correlation in developmental psychopathology. *Dev Psychopathol*. 2013;25:1-6.

5.4.1 Discussão Artigo 4

Este estudo teve por objetivo investigar a influência genética na etiologia da irritabilidade. Além disso, examinamos como fatores ambientais afetam as influências genéticas. Como não existem estudos genéticos específicos para irritabilidade, selecionamos genes candidatos com evidências de associação com aspectos fenotípicos, particularmente de temperamento, relacionados à irritabilidade.

Nossos resultados demonstraram influência genética na etiologia da irritabilidade através de um escore poligênico. O escore poligênico foi preditor de irritabilidade mesmo após o controle de fatores ambientais.

Uma possível justificativa para a positividade dos nossos resultados é de que como não haviam estudos anteriores, isto nos possibilitou abranger polimorfismos relacionados a múltiplos comportamentos e precursores de inúmeros processos psicopatológicos, assim como a irritabilidade.

Possivelmente existe uma correlação gene ambiente (rGE), onde uma maior carga genética aciona negativamente o ambiente, gerando um ciclo psicopatológico que se retroalimenta e que perpetua o comportamento disfuncional, i.e. irritabilidade.

6. ANEXOS

6.1 Artigo 5

Bipolar disorder and disruptive mood dysregulation in children and adolescents:
assessment, diagnosis and treatment

6.2 Capítulo 1

Temperament and vulnerability to externalizing behavior

6.1 Artigo 5

“Bipolar disorder and disruptive mood dysregulation in children and adolescents: assessment, diagnosis and treatment”

Bipolar disorder and disruptive mood dysregulation in children and adolescents: assessment, diagnosis and treatment

Fernanda Valle Krieger and Argyris Stringaris

Evid Based Mental Health published online June 8, 2013
doi: 10.1136/eb-2013-101400

Updated information and services can be found at:
<http://ebmh.bmj.com/content/early/2013/06/07/eb-2013-101400.full.html>

These include:

References

This article cites 17 articles
<http://ebmh.bmj.com/content/early/2013/06/07/eb-2013-101400.full.html#ref-list-1>

P<P

Published online June 8, 2013 in advance of the print journal.

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections

Articles on similar topics can be found in the following collections

[Bipolar disorder](#) (197 articles)
[Depressive disorder](#) (502 articles)
[Drugs: psychiatry](#) (292 articles)
[Attention-deficit hyperactivity disorder](#) (96 articles)
[Neurology](#) (966 articles)
[Epidemiology](#) (1387 articles)

Advance online articles have been peer reviewed, accepted for publication, edited and typeset, but have not yet appeared in the paper journal. Advance online articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Advance online articles must include the digital object identifier (DOIs) and date of initial publication.

To request permissions go to:
<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:
<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:
<http://group.bmj.com/subscribe/>

Bipolar disorder and disruptive mood dysregulation in children and adolescents: assessment, diagnosis and treatment

doi:10.1136/eb-2013-101400

Bipolar disorder (BD) is a heritable psychiatric condition, that is, associated with lifelong distress and impairment. There has been a long-standing interest in the early-life origins of BD, not least because as many as 50% of adults with BD report onset of their symptoms during childhood and adolescence.¹ In this article, we present evidence on the assessment and treatment of BD and related conditions in young people. We also discuss the recent controversy about BD in children and adolescents that has led to the introduction of the diagnosis of disruptive mood dysregulation disorder (DMDD) by the Diagnostic and Statistical Manual for Mental Disorders (DSM)-5.

MANIA

Diagnostic features

BD is characterised by episodes, that is, distinct periods of abnormally and persistently elevated, expansive or irritable mood. During these episodes, patients experience symptoms such as grandiosity, distractibility, decreased need for sleep, pressure of speech, an increase in activity, flight of ideas and psychomotor agitation. These episodes are required to last by at least 4 days to diagnose hypomania or at least 7 days to diagnose mania. The insistence on episodic mood changes is crucial and prevents clinicians from rating symptoms such as the chronic concentration problems of a child with attention deficit hyperactivity disorder (ADHD) as evidence for mania.² Manic episodes are extremely rare in children and relatively rare in adolescents according to epidemiological studies in the UK and the USA.³

Acute treatment

Pharmacotherapy is the mainstay of treatment for acute mania. Aripiprazole, quetiapine and risperidone are approved by the US Food and Drug Administration (FDA) for the treatment of mania in children and adolescents, and olanzapine is approved only for adolescents. A comparative analysis of randomised, placebo-controlled trials in youth BD established that atypical antipsychotics have better efficacy and tolerability compared with anticonvulsants and lithium (effect size atypical antipsychotics 0.65, CI 0.53 to 0.78 vs anticonvulsants and lithium 0.24, 95% CI 0.06 to 0.41). Particularly in youth, atypical antipsychotics caused significantly more weight gain than anticonvulsants (effect size atypical antipsychotics 0.53, CI 0.41 to 0.66 vs anticonvulsants 0.10, CI 0.12 to 0.33).⁴

Maintenance treatment

The goal of maintenance treatment is mood stabilisation; keeping symptom improvements of acute treatment, and preventing recurrence of episodes. Assessment of residual symptoms, treatment adherence and side effects are part of relapse prevention. The only long-term trial in youth with BD is a 30-week, randomised controlled trial showing that aripiprazole was superior to placebo in improving mania symptoms at endpoint.⁵ However, completion rates were low (32.4%), limiting the inferences that can be drawn about it. We need more

evidence of maintenance treatment in young people with BD. This is particularly important because of the potentially serious long-term side effects of antipsychotic medication.

Adjunctive psychosocial and familial interventions might play an important role in relapse prevention of youth BD. Family-focused treatment (FFT) is a psychoeducational intervention designed to reduce familial stress, conflict and affective arousal by enhancing communication and problem-solving among patients and caregivers, and it appears to ameliorate the course of BD in adolescents.⁶

BIPOLAR DEPRESSION

Many young people with BD will present with symptoms of depression before experiencing a full-blown manic episode and may spend more time of their illness being depressed than manic. It appears that youth with bipolar depression have more severe depressive episodes, associated with suicidality, hopelessness, and anhedonia compared with youth with unipolar depression,⁷ although further studies are required to distinguish between the two.

Psychological treatment

Preliminary results on cognitive behavioural therapy (CBT) for bipolar depression have shown a significant decrease in depressive symptoms. Given the evidence for effectiveness of CBT in unipolar depression, it seems reasonable to offer CBT for BD depression. The use of CBT adjunctive to pharmacotherapy or alone should rely on intensity of symptoms, level of impairment and cognitive resources of the patient.⁷

FFT has also shown promising results. In a randomised trial comparing effectiveness of FFT with enhanced care (only psychoeducation) in addition to pharmacotherapy in adolescents, the FFT group recovered faster from depressive symptoms, spent fewer weeks in depressive episodes and had a more favourable trajectory of depression symptoms for 2 years.⁶

Pharmacological treatment

There is no FDA-approved medication for bipolar depression in children and adolescents. Medications used to treat bipolar depression in adults are commonly used in the treatment of children and adolescents. Quetiapine is an effective treatment of depressive episodes in adults with BD, and it seems reasonable to use this medication in older adolescents with BD.

SHORT-LIVED MANIC EPISODES

The duration requirement—a minimum of 7 days for mania or 4 days for hypomania is arbitrary and has been challenged in the literature about adults with BD.⁸ Moreover, it has been argued that shorter episodes may be more characteristic of mania in children. Episodes of shorter duration (between 1 and 3 days) during which young people experience manic symptoms are certainly much more common than classical (hypo-) mania in general population samples.³ In addition, evidence from longitudinal clinical studies suggests that up to 40% of people who experience such shorter episodes (often termed BD-not otherwise specified, BD-NOS) may go on to develop classical (4–7 days) BD.⁹ However, more evidence is required to decide whether these short-lived episodes of mania-like symptoms are aetiologically linked with BD.

Treatment

There is no trial evidence available for the treatment of such episodes. These episodes, which can often cause substantial impairment, can present a challenge to clinicians. We monitor

Expert review

such patients closely using weekly mood monitoring and offer several sessions of psychoeducation to them and their family where we explain the relative merits of available treatment options. In our own experience, treatment of comorbid conditions (eg, ADHD) and family-based interventions or CBT can help reduce the frequency of such episodes. Typically, we reserve treatment with antimanic agents only for those who fall short of the duration requirement by a small margin, for example, children with clear manic symptoms lasting for 3 days, or those who have been resistant to other treatment options.¹⁰

BIPOLAR CONTROVERSY: IRRITABILITY AND DISRUPTIVE MOOD DYSREGULATION DISORDER

Over the last 20 years, there has been a dramatic—up to 500%—increase in the diagnosis of BD in children and adolescents in the USA.² At the same time, there was a steep rise in antipsychotic prescriptions in the USA,¹¹ raising concerns that children were overdiagnosed and unduly prescribed potentially harmful medication. The observed increase is unlikely due to a genuine increase in the prevalence of the disorder, but rather reflect changes in diagnostic practice. In particular, it has been argued² that children presenting with severe irritability without clear-cut episodes have been mislabelled as suffering from BD. Such chronic irritability needs to be contrasted to episodic mood change (either elation or irritability or depression, as discussed above) that lasts several days to a few weeks and is typical of bipolar disorder. To test the claim that children with severe chronic irritability had an early form of BD, Leibenluft *et al* created a new category entitled Severe Mood Dysregulation (SMD), that has chronic negative mood in the form of irritability and frequent temper outbursts as its symptoms. Several studies have shown that chronic and episodic irritability follow distinct trajectories; episodic symptoms are associated with mania, whereas chronic symptoms are strongly associated with unipolar depression and anxiety.¹² Longitudinally, episodic irritability in early adolescence was associated with generalised anxiety disorder (GAD) and mania in late adolescence, and only mania in adulthood, whereas chronic irritability in early adolescence was associated with disruptive behavioural disorders in late adolescence and only major depressive disorder (MDD) in adulthood.¹³ Individuals with episodic and elated mood are up to 50 times more likely to develop mania than those with chronic irritability in a 3-year follow-up.¹⁴

On the basis of the research on SMD, and the importance of chronic irritability for developmental psychiatry, the DSM-5 working group proposed a new diagnostic category called DMDD. The definition of this new category resembles the one for SMD (severe recurrent temper outbursts superimposed on persistently irritable or angry mood); however, DMDD does not include the hyperarousal requirement of SMD. There is still little evidence on DMDD itself so far, although the announcement by the DSM has led to concerns that normative children's behaviours (tantrums) would be pathologised. Recently Copeland *et al*,¹⁵ using two community samples, suggested that DMDD was relatively rare, ranging from 0.8% to 3.3%, with higher rates in preschool age and in boys. In the same study, DMDD significantly cooccurred with all common psychiatric disorders particularly with depressive disorders (OR between 9.9 and 23.5) and oppositional defiant disorder (OR between 52.9 and 103.0).

It remains unclear whether severe irritability should be declared a disorder or seen as the extreme of a spectrum.¹⁶ Empirical evidence supports chronic irritability as a continuum; however, clinical decisions require thresholds and binary disease

categories are commonly used for such purposes in many other disorders.

Treatment

With regard to pharmacological options for the treatment chronic irritability, the only randomised controlled trial in children with SMD found no benefit of lithium over placebo. An open-label trial using low doses (mean 1.2 ± 0.5 mg) of risperidone in children and adolescents with SMD showed significant reductions in irritability scores.¹⁷

Parental intervention (based on Webster-Stratton techniques) seems to have a beneficial effect on children with oppositional defiant disorder and may be particularly suitable for children with irritability, although this needs to be tested further.¹⁸

Fernanda Valle Krieger,¹ Argyris Stringaris²

¹Department of Psychiatry, University of São Paulo, São Paulo, Brazil

²King's College London, Institute of Psychiatry, London, UK

Competing interests None.

REFERENCES

1. **Perlis RH**, Dennehy EB, Miklowitz DJ, *et al*. Retrospective age at onset of bipolar disorder and outcome during two-year follow-up: results from the STEP-BD study. *Bipolar Disord* 2009;**11**:391–400.
2. **Leibenluft E**. Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. *Am J Psychiatry* 2011;**168**:129–42.
3. **Stringaris A**, Santosh P, Leibenluft E, *et al*. Youth meeting symptom and impairment criteria for mania-like episodes lasting less than four days: an epidemiological enquiry. *J Child Psychol Psychiatry* 2010;**51**:31–8.
4. **Correll CU**, Sheridan EM, DelBello MP. Antipsychotic and mood stabilizer efficacy and tolerability in pediatric and adult patients with bipolar I mania: a comparative analysis of acute, randomized, placebo-controlled trials. *Bipolar Disord* 2010;**12**:116–41.
5. **Findling RL**, Youngstrom EA, McNamara NK, *et al*. Double-blind, randomized, placebo-controlled long-term maintenance study of aripiprazole in children with bipolar disorder. *J Clin Psychiatry* 2012;**73**:57–63.
6. **Miklowitz DJ**, Buickians A, Richards JA. Early-onset bipolar disorder: a family treatment perspective. *Dev Psychopathol* 2006;**18**:1247–65.
7. **DeFilippis M**, Wagner KD. Bipolar depression in children and adolescents. *CNS Spectr*. Published online: April 2013:1–5. doi:10.1017/S1092852913000217
8. **Angst J**. Problems in the current concepts and definitions of bipolar disorders. *World Psychiatry* 2011;**10**:191–2.
9. **Birmaher B**, Axelson D, Goldstein B, *et al*. Four-year longitudinal course of children and adolescents with bipolar spectrum disorders: the Course and Outcome of Bipolar Youth (COBY) study. *Am J Psychiatry* 2009;**166**:795–804.
10. **Leigh E**, Smith P, Milavic G, *et al*. Mood regulation in youth: research findings and clinical approaches to irritability and short-lived episodes of mania-like symptoms. *Curr Opin Psychiatry* 2012;**25**:271–6.
11. **Offson M**, Crystal S, Huang C, *et al*. Trends in antipsychotic drug use by very young, privately insured children. *J Am Acad Child Adolesc Psychiatry* 2010;**49**:13–23.
12. **Stringaris A**, Zavos H, Leibenluft E, *et al*. Adolescent irritability: phenotypic associations and genetic links with depressed mood. *Am J Psychiatry* 2012;**169**:47–54.
13. **Krieger FV**, Polanczyk GV, Goodman R, *et al*. Dimensions of oppositionality in a Brazilian community sample: testing the DSM-5 proposal and etiological links. *J Am Acad Child Adolesc Psychiatry* 2013;**52**:389–400.
14. **Stringaris A**, Baroni A, Haimm C, *et al*. Pediatric bipolar disorder versus severe mood dysregulation: risk for manic episodes on follow-up. *J Am Acad Child Adolesc Psychiatry* 2010;**49**:397–405.
15. **Copeland WE**, Angold A, Costello EJ, *et al*. Prevalence, comorbidity, and correlates of DSM-5 proposed disruptive mood dysregulation disorder. *Am J Psychiatry* 2013;**170**:173–9.
16. **Stringaris A**, Goodman R, Ferdinando S, *et al*. The affective reactivity index: a concise irritability scale for clinical and research settings. *J Child Psychol Psychiatry* 2012;**53**:1109–17.
17. **Krieger FV**, Pheula GF, Coelho R, *et al*. An open-label trial of risperidone in children and adolescents with severe mood dysregulation. *J Child Adolesc Psychopharmacol* 2011;**21**:237–43.
18. **Scott S**, O'Connor TG. An experimental test of differential susceptibility to parenting among emotionally-dysregulated children in a randomized controlled trial for oppositional behavior. *J Child Psychol Psychiatry* 2012;**53**:1184–93.

6.2 Capítulo 1

“Temperament and vulnerability to externalizing behavior”

Oxford Handbooks Online

Temperament and Vulnerability to Externalizing Behavior

Fernanda Valle Krieger and Argyris Stringaris

The Oxford Handbook of Externalizing Spectrum Disorders (*Forthcoming*)

Edited by Theodore P. Beauchaine and Stephen P. Hinshaw

Online Publication Date: Dec
2014

Subject: Psychology, Clinical Psychology
DOI: 10.1093/oxfordhb/9780199324675.013.002

Abstract and Keywords

Temperamental traits are defined as early developing, biologically rooted behavioral and emotional tendencies that are stable across situations and time and play an important role in the etiology, manifestation, and maintenance of most common emotional and behavioral disorders. This chapter examines the role of individual differences in temperament as vulnerabilities to externalizing behavior problems in children, adolescents, and adults. First, different models of temperament and general pathways to psychopathology are described. Then, specific temperamental traits that are associated with externalizing problems and their likely underlying mechanisms are detailed. This chapter provides a critical view of the complexity of interactions and correlations among temperament, genetics, and environmental factors that may increase the risk for externalizing behaviors.

Keywords: temperament, negative affect, emotionality, effortful control, fearfulness, irritability, externalizing behavior

Children differ markedly from one another in their behavioral responses to external events. One child may be fearful and cry at even moderately stimulating play, whereas another may enjoy vigorous play and seek out exciting events. One child may be reserved, whereas another may be exuberant. Some children are described as aggressive, yet others are gentle. From early infancy, children show considerable variability in their reactions to the environment. Similar stimuli may evoke distinct reactions across individuals, whereas diverse stimuli may evoke similar response within the same individual (Shiner & Caspi, 2003). Temperamental traits are defined as early developing, biologically rooted behavioral and emotional tendencies that manifest particularly (but not exclusively) in social interactions and that are relatively stable over time and across situations (e.g., Goldsmith et al., 1987).

Temperamental characteristics also follow developmental differentiation. For example, newborns show primarily distress and avoidance movements. By age 3 months, however, anger and frustration are evidenced concomitantly with approach reactions such as smiling, laughter, and body movement (Bridges, 1932). Physical approach preferences are observed between ages 4–6 months as motor systems develop (Rothbart, 2007). Fear (behavioral inhibition) differentiates from general stress proneness by age 7–10 months (e.g., Bridges, 1932; Kagan, 2013).

Temperamental constructs capture observed behavior regardless of underlying motivations or content. Therefore, temperament represents the *how* of behavior; that is, the style or form of behavior, distinct from the *why*, which addresses the motivational component, and the *what*, which addresses the content or ability (Goldsmith et al., 1987; Rutter, 1987). Temperamental elements include the amount of energy to kick, persistence in trying to reach toys, and intensity of reactions when objectives are not accomplished (level of fussing or crying). All of these behavioral and emotional tendencies vary along key dimensions (Goldsmith et al., 1987), with implications for later development and vulnerability to psychiatric morbidity (Kagan, 2013; Rutter, 1987). Children vary in their propensity to develop psychopathology, and temperament plays an important role in the etiology, manifestation, and maintenance of most common emotional and behavioral disorders (Muris & Ollendick, 2005; Rettew, 2013).

In this chapter, we examine the role of individual differences in temperament as vulnerabilities to externalizing behavior problems in children, adolescents, and adults. In the first section, we describe broad aspects of temperament and summarize different models of temperament and general pathways to psychopathology. In the next section, we detail specific temperamental traits that are associated with externalizing problems, and we examine likely mechanisms underlying these associations.

General Concepts of Temperament

Models of Child Temperament

Among diverse concepts of temperament, three key components are common to most widely accepted definitions. First, temperament manifests very early in life, from infancy onward. Second, temperament is influenced considerably by genetic and other heritable factors. Third, temperament shows at least moderate stability across time (Cloninger, 2004; Lemery, Goldsmith, Klinnert, & Mrazek, 1999; Zentner & Shiner, 2012). Nevertheless, there is still controversy among specialists on the precise structure of temperament. Here, we briefly summarize the most widely used models and discuss similarities among them (Zentner & Bates, 2008).

In 1966, Chess and Thomas described the structure of temperament using nine dimensions (Chess & Thomas, 1966), including (1) *activity level*, which refers to the motor component of a child's functioning; (2) *rhythmicity*, which is the predictability of any function in time; (3) *approach* or *withdrawal*, which comprise the initial response to a novel stimulus; (4) *adaptability*, or characteristic responding to changes in the environment; (5) *threshold of responding*, or the intensity of stimulation required to evoke a response; (6) *intensity of reaction*, which refers to the energy level of a response; (7) *quality of mood*, or the amount of pleasant and joyful behavior in contrast to unpleasant, unfriendly behavior; (8) *distractibility*, which refers to how extraneous stimuli alter ongoing behavior, and (9) *attention span* and *persistence*, or the length of time an activity is pursued in the face of obstacles.

Combinations of these categories lead to three fundamental temperament types. The first, "easy temperament," is characterized by regularity, positive responses to new stimuli, high adaptability, and a preponderantly positive mood. The second, "difficult temperament," is marked by signs of irregularity, negative withdrawal responses to new stimuli, slow adaptability to changes, and predominantly negative mood expressions. The third, "slow-to-warm-up," refers to children who exhibit negative responses to new stimuli but adapt progressively after repeated contact (Thomas & Chess, 1977).

In contrast to Chess and Thomas (1966), Buss and Plomin proposed the Emotionality-Activity-Sociability (EAS) model (Buss & Plomin, 1975, 1984). According to this conceptualization, *emotionality* is characterized by psychological instability and proneness to fear, anger, and sadness; *activity* refers to characteristics such as tempo and vigor; and *sociability* refers to tendencies to affiliate with and be responsive to others (Buss & Plomin, 1984).

Rothbart and colleagues' model defines temperament as a set of individual differences in reactivity and self-regulation (Rothbart, 1981; Rothbart & Ahadi, 1994). Reactivity refers to physiological excitability of neural systems, whereas self-regulation refers to processes that promote both volitional and automatic control over behavior. The combination of these constructs results in three broad dimensions, including *negative affectivity*, which reflects a tendency to experience negative emotions; *surgency*, which refers to social orientation, motor activity, and a tendency to experience positive emotions; and *effortful control*, which includes inhibitory control and attentional focusing (Rothbart & Ahadi, 1994).

According to Kagan (e.g., Kagan, Reznick, & Snidman, 1987) individual differences in behavioral reactions to unfamiliarity, threat, and challenge are due to tonic differences in neurobiological substrates of reactivity (amygdala, hypothalamus, and pituitary-adrenal axis). For example, children with a low threshold to initiate a neurophysiological response in the face of novel stimuli present as behaviorally *inhibited*—or with tendencies to display fear, distress, and avoidance.

An integrative perspective encompassing basic temperamental components in childhood is suggested by Zentner and Bates (2008). It includes (1) *behavioral inhibition/fear*, or inhibition of behavior in response to novel or unfamiliar people and situations; (2) *irritability/frustration*, defined as aggressive or irritated behavior in response

Temperament and Vulnerability to Externalizing Behavior

to painful and/or frustrating events; (3) *positive emotionality*, the propensity to experience positive emotions typically associated with approach behaviors; (4) *activity level*, or the frequency, speed, and vigor of gross motor movements and locomotion, as well as intolerance of enforced idleness; (5) *attention/persistence*, defined as the capacity for attentional focusing and control as a basis for voluntary behavior including persistence; and (6) *sensory sensitivity*, or proneness to sensory (e.g., visual, auditory) discomfort.

Although there are several differences across these models, there is increasing support for a tripartite theory of temperament among children (Chorpita, Plummer, & Moffitt, 2000; Rettew, 2013). Activity level is represented clearly in each of the temperament models. Emotionality is correlated highly with both adaptability/mood and negative affectivity and correlated moderately with social fearfulness (Zentner & Shiner, 2012). Factor analysis of the Infant Behavior Record (IBR), an observational measure of infant temperament, yields three dimensions found in most systems: activity, task orientation (attention span and persistence), and affect-extraversion (positive emotionality and sociability; Matheny, 1980). In addition, a theoretical distinction between reactive temperaments (emotionality, activity, sociability, and positive/negative affect) and regulatory temperaments (effortful control, inhibitory control, behavioral inhibition, and attentional focusing) has been proposed (Rothbart, 2007). However, the degree to which reactivity can be separated from regulation on the basis of behavioral measures is open to debate.

A potential consensus framework suggests a hierarchical structure of temperament, wherein high-order traits reflect underlying, basic systems of reactivity, from which emerge “lower order” traits (see, e.g., Nigg, 2006). At the top of the hierarchy are two incentive factors: approach and withdrawal. Approach is defined as willingness to approach potential rewarding contexts and is associated with reinforcement learning. Lower order traits associated with approach include positive emotionality, sociability, and activity level (Shiner & Caspi, 2003). In contrast, withdrawal is defined as promptness of avoidance of possible unrewarding or uncertain situations and is associated with affective reactivity, fear, and sadness (Nigg, 2006).

*Adapted from Nigg, 2006

[Click to view larger](#)

Figure 1 . A model in which temperament comprises of both higher order (approach, withdrawal) and lower order (activity, emotionality) behavioral tendencies.

A second-order factor is comprised of behavioral responses including reactivity and effortful control (Eisenberg & Spinrad, 2004). Effortful control is the ability to inhibit a dominant response and activate a subdominant response. It includes elements of attentional control, attentional shifting, and focusing behavior (Rothbart, 2007). Effortful control is related to executive functions and involves top-down modulation of motivational response systems (approach, withdrawal). Reactive control is defined as the relatively automatic suppression of behavioral and emotional expression. Reactive control is less associated with executive functions and is related conceptually to low approach and high withdrawal (Eisenberg & Spinrad, 2004). Data indicate that effortful control is closely related to conscientiousness, whereas reactive control represents broad regulatory processes (Nigg, 2006). Nevertheless, the hierarchical framework suggests that the interplay between approach/withdrawal systems and reactive/effortful controls leads to distinct temperamental traits. For example, high levels of approach can be associated with either high levels of reactive control (prosocial behaviors) or low levels of reactivity control (anger) (Eisenberg & Spinrad, 2004; Carver & Harmon-Jones, 2009). Figure 1 displays a schematic hierarchical model.

Models of Adult Temperament

Consistent with the hierarchical perspective, adult personality researchers emphasize the importance of a few higher order factors rather than a large number of more specific traits in conceptualizations of adult temperament. Among various models for adult personality is the five-factor model (Big Five), which includes five broad dimensions: (1) *neuroticism*, (2) *extraversion*, (3) *openness*, (4) *agreeableness* and, (5) *conscientiousness* (Digman, 1990). Although associations between adult personality and temperament have long been a source of debate, given the increasing role of socialization on behavior across development, Cloninger (1987) proposed a three-factor model of adult personality that is rooted in neurobiological substrates of approach, withdrawal, and social affiliation. Cloninger's model comprises *novelty seeking*, *harm avoidance*, *reward dependence*, and *persistence*. Later, Cloninger complemented his model of temperament by including self-directedness, cooperativeness, and self-transcendence as additional domains required to fully capture adult personality (Cloninger, 2004).

Although Cloninger's (1987) conceptualization provides a particularly good example of an adult temperament model, others also specify at least three high-order dimensions, including (1) approach, as manifested generally in expressions of positive emotion; (2) avoidance, as manifested generally in expressions of negative emotion; and (3) constraint, as manifested in tendencies to control expressions of emotion and behavioral impulses (Shiner & Caspi, 2003).

Genetic Influences on Temperament

Behavioral genetic studies estimate the extent to which heritable and environmental influences contribute to behavioral variability (Saudino, 2005; Jones & Smith, this volume). This methodology involves decomposing phenotypic variation into heritable and environmental components. *Heritability* is the proportion of phenotypic variance that can be attributed to heritable factors.¹ The remaining variance is attributed to environmental factors, which comprise *shared environmental* effects (familial resemblances that are not explained by genetic factors) and *nonshared environmental* effects (environmental influences that are unique to each individual, along with measurement error (see Beauchaine & Gatzke-Kopp, 2013; Plomin, DeFries, & McClearn, 2001; Chapter 8). Twin and adoptive/nonadoptive sibling designs are the methodological approaches most frequently used to disentangle heritable and environmental influences on behavior (Plomin et al., 2001). However, influences of environment on temperament are complex—and become more so over time—because they involve dynamic interplay of genes and environment (Plomin, DeFries, & Loehlin, 1977). Evidence for gene $\times$ environment (G $\times$ E) interactions in the expression of temperament and psychopathological trajectories is detailed later (gene-environment correlations [rGE] may be relevant as well).

Most behavioral genetics studies of temperament yield moderate to high heritability coefficients (Goldsmith, Lemery, Buss, & Campos, 1999; Saudino, 2005), although rates of heritability vary across ages (Goldsmith et al., 1999). There is evidence of very low heritability in the neonatal period (Riese, 1990). Heritability increases from early to middle childhood across a variety of temperamental traits (Cyphers, Phillips, Fulker, & Mrazek, 1990; Goldsmith, Buss, & Lemery, 1997). By toddlerhood, heritability is substantial, with h^2 estimates indicating that heritability accounts for 20–60% of the variance in temperamental traits (Hicks, Krueger, Iacono, McGue, & Patrick, 2004; Plomin et al., 1993). Among toddlers, heritability of effortful control is estimated to be 58%, with estimates of 42% for negative affect and 41% for extraversion/surgency (Goldsmith et al., 1997).

Such broad ranges in heritability result from a number of factors, including methodological issues, such as random sampling error, influences of assessment instruments and observers (Saudino, 2005), and the consistent finding that heritabilities of nearly all human behavioral traits (including psychopathology) rise across development (see Beauchaine & Gatzke-Kopp, 2013; Bergen, Gardner, & Kendler, 2007). For our purposes, it is particularly important to note differences in heritability estimates based on parent ratings versus other observer ratings. Studies based on parent ratings of temperament commonly show greater gaps between monozygotic (MZ) and dizygotic (DZ) twin correlations (Stevenson & Fielding, 1985) signifying higher estimates of heritability. Parent-rating MZ correlations are typically moderate, whereas DZ correlations are much lower than expected (< 50% of MZ correlations). In contrast, when temperament is assessed objectively via observer ratings, high heritability is still evident, but low DZ correlations do not emerge (Plomin et al., 1993). In fact, very low DZ resemblance and higher heritability estimates occur only when parent-rating measures are used, and these are likely to emanate from contrast effects—rater biases that exaggerate the differences between DZ twins. In other words, parents may be

especially likely to perceive DZ twins as having differing temperaments (Braungart, Plomin, DeFries, & Fulker, 1992; Saudino, McGuire, Reiss, Hetherington, & Plomin, 1995). This artifact can result in overestimates of heritability in twin studies. Nevertheless, moderate heritability based on parent ratings is supported by similar findings with more objective measures. Therefore, there is little space for doubt that temperament is heritable (Saudino, 2005).

Because child temperament is only partly heritable, environmental factors must account for the remaining variance. Indeed, research shows consistent associations between family environment and children's temperament (Lemery-Chalfant, Kao, Swann, & Goldsmith, 2013; Leventhal & Brooks-Gunn, 2000). For example, a chaotic, unstructured home typically does not support development of foundational skills such as self-regulation (Baumrind, 1993; Dumas et al., 2005; Wachs, 1988). Importantly, however, influences of environment on temperament are complex, involving interactions with genes. We discuss such gene-environment interplay later, in the section on moderators of temperament.

Sex Differences

In a meta-analysis, Else-Quest and colleagues (2006) estimated magnitudes of sex differences in dimensions of temperament among children between ages 3 months and 13 years. Three broad dimensions, including effortful control, negative affectivity, and surgency were examined. A large sex difference was found for effortful control favoring girls (weighted effect size (d) = -1.01 , 95% confidence interval [CI] = -1.37 to -0.64 , $p < 0.05$). Thus, girls have greater ability to manage and regulate their attention and inhibit their impulses than do boys. In contrast, boys exhibit greater surgency ($d = 0.55$, 95% CI = 0.22 – 0.89 , $p < 0.05$) and are therefore more active, less shy, and derive more pleasure from high-intensity stimuli than do girls. There was no sex difference in negative affectivity, indicating that boys and girls do not differ significantly in the extent to which they are difficult, emotionally reactive, or soothable. Analyses of potential moderators such as age, socioeconomic status, and source of assessment showed no significant interactions with sex.

Temperament and Vulnerability to Psychopathology

Development is affected continuously by causal processes that occur across various levels of analysis (see Cicchetti, 2008). Cultural, socioeconomic, and community-level influences are considered distal factors, whereas family relationships and parenting represent proximal factors. Risk factors present within these contexts may increase risk for psychopathology throughout development. However, individual differences also affect one's risk for psychiatric disorders and may moderate (i.e., interact with) effects of environmental risk. Among such individual differences, temperament affects children's vulnerability or resilience to psychopathology (e.g., Lengua & Wachs, 2012).

Rather than simply describe mere correlations, it is essential to examine how temperament and psychopathology are linked causally, including the specification of intervening variables (see Frick, 2004; Hoyle, 2000). Shiner and Caspi (2003) suggest distinct processes through which temperament might be associated with concurrent or future psychopathology. One such process is "spectrum association," whereby psychopathology represents the severe end of continuously distributed temperamental traits. For example, some have argued that attention-deficit/hyperactivity disorder (ADHD) lies at the extreme end of temperamental impulsivity and is therefore not a discrete condition (Jensen et al., 1997). Others have suggested "vulnerability association" (Lahey, 2004; Lengua, West, & Sandler, 1998), whereby certain temperamental traits increase risk for psychopathology through interactions with independent processes such as learning (e.g., reinforcement, punishment; Kochanska, 1997), environmental risk exposure (e.g., maltreatment, neighborhood violence/criminality; Lynam et al., 2000; Owens, Shaw, & Vondra, 1998), or environmental selection (i.e., active rGE; Scarr & McCartney, 1983).

Such processes are dynamic and multifaceted, involving interactions between individual-level vulnerabilities (in this case temperament) and exogenous influences such as family risk, culture, and socioeconomic status. Complex interactions between individual vulnerabilities and environmental risk factors—the mechanisms by which temperament shapes environment and vice versa—may end up contributing to development of psychopathology.

Temperament and Pathways to Externalizing Behavior

A vast literature provides evidence for associations between certain temperamental styles and externalizing behaviors (Rettew, 2013; Rettew, Copeland, Stanger, & Hudziak, 2004). Associations between temperament and externalizing problems have been found among preschool children (Hirshfeld-Becker et al., 2002), school-aged children (Blackson, Tarter, Martin, & Moss, 1994), and adolescents (Giancola, Mezzich, & Tarter, 1998). Prospective studies indicate that dimensions of temperament measured early in life predict externalizing problems later—in preschool (Keenan, Shaw, Delliquadri, Giovannelli, & Walsh, 1998), in childhood (Raine, 2002), into adolescence (Caspi & Silva, 1995), and beyond.

In this section we examine three mechanisms through which temperament is associated with externalizing behaviors (Frick & Morris, 2004; Kochanska, Barry, Jimenez, Hollatz, & Woodard, 2009; Nigg, 2006). The first pathway involves negative affectivity, in which irritability plays a critical role. The second pathway involves deficient development of empathy and may be mediated by low trait anxiety/fearfulness. The third pathway involves low effortful control and deficient inhibition. Here, we describe each pathway and relevant mechanisms related to externalizing behaviors.

Negative Emotionality

Negative emotionality is a heritable individual difference (see earlier discussion). As children develop, their tendencies to react disproportionately to environmental events with strong emotions of negative valence may indicate and predict a failure to acquire adequate emotional regulatory abilities and therefore confer risk for psychopathology (Eisenberg et al., 2001; Hoeksma, Oosterlaan, & Schipper, 2004). Vulnerability to externalizing behaviors through negative affectivity involves low reactive control (Carver & Harmon-Jones, 2009). Thus, anger, irritability, defiance, and reactive aggression become progressively problematic, as manifested in oppositional behaviors and conduct problems (Hubbard et al., 2002).

Diverse temperamental traits characterized by high negative reactivity show associations with externalizing behaviors (Eisenberg et al., 2001). Chess and Thomas's "difficult temperament" (irregularity, negative withdrawal responses to new stimuli, slow adaptability to change, and negative emotionality) can be interpreted as similar to negative reactivity. Children who score high on indices of a difficult temperament are at high risk for conduct problems (Keenan et al., 1998; Kingston & Prior, 1995). Similarly, Buss and Plomin's "emotionality" predicts oppositional defiant disorder (ODD; Burke, Waldman, & Lahey, 2010), particularly ODD and comorbid internalizing behaviors (Stringaris, Maughan, & Goodman, 2010).

In fact, temperamental traits characterized by high negative emotional reactivity are associated strongly not only with externalizing behaviors but also with childhood mental disorders in general. They may be central to understanding the overlap between externalizing and internalizing disorders (see Chapter 26). This hypothesis suggests that associations between two dimensions (or, categorically, two disorders) reflect differing manifestations of common underlying vulnerability (Angold, Costello, & Erkanli, 1999). Indeed, heritable contributions to comorbidity between major depressive disorder and conduct disorder (CD) are shared with genetic influences on negative emotionality (Tackett, Waldman, Van Hulle, & Lahey, 2011). Crucially, after accounting for heritable influences on negative emotionality, heritable influences on this comorbidity are not significant, suggesting that the overlap between the two disorders may derive from heritable influences on temperament.

Additional support for the centrality of negative emotionality to psychopathology comes from studies addressing irritability. Defined as a low threshold to experience anger in response to frustration, irritability is akin conceptually to negative emotionality or negative reactivity (Leibenluft, Blair, Charney, & Pine, 2003). Irritability is present in a wide range of disorders in childhood such as ODD, CD, major depression disorder, ADHD, depression, and anxiety (Krieger, Leibenluft, Stringaris, & Polanczyk, 2013a). Evidence suggests that irritability is associated with a family history of depression and that shared genetic factors underlie both irritability and depression (Krieger et al., 2013b; Stringaris, Zavos, Leibenluft, Maughan, & Eley, 2012). Moreover, chronic irritability among youth predicts depression 20 years later (Stringaris, Cohen, Pine, & Leibenluft, 2009). In short, irritability is likely to be a crucial concept to understanding trajectories from temperamental precursors and later mental disorders in children, adolescents, and adults (Aebi, Plattner, Metzke, Bessler, & Steinhausen, 2013; Rowe, Costello, Angold, Copeland, & Maughan, 2010; Stringaris & Goodman, 2009a, 2009b).

Low Fearfulness

Deficits in emotion regulation explain considerable variance in conduct problems and aggression that are displayed in the context of high emotional arousal (Beauchaine, Gatzke-Kopp, & Mead, 2007; Hubbard et al., 2002; Shields & Cicchetti, 1998). A second type of aggression is referred to as *instrumental* or *premeditated*. Low levels of fearful inhibition and the presence of callous-unemotional traits predict this type of aggression (Shaw, Gilliom, Ingoldsby, & Nagin, 2003).

Moral socialization is partly dependent on negative arousal (i.e., anxiety) evoked by potential punishment. Internalization of social norms occurs when children experience negative arousal when confronted with a forbidden activity. Thus, without fearful inhibition, it is more difficult for a child to develop moral socialization, empathy, and guilt (Moul & Dadds, 2013; Newman, Patterson, & Kosson, 1987). In turn, lack of empathy and guilt are believed to underlie psychopathic behaviors. In a large sample of children from Mauritius, Gao and colleagues (2010) found that crime at age 23 retrospectively predicted poor fear conditioning at age 3.

Youth with callous-unemotional traits also present characteristics consistent with low levels of fearful inhibition (Barry et al., 2000; Chapter 22). Compared to those with low callous-unemotional traits, children with callous-unemotional traits show a more severe and aggressive pattern of conduct problems and are more likely to engage in instrumental/premeditated forms of aggression (Frick, Ray, Thornton, & Kahn, 2014; Loney, Frick, Clements, Ellis, & Kerlin, 2003). Furthermore, they exhibit deficits in responses to punishment and in reactivity to threatening stimuli, which also suggests deficient fearful inhibition (Barker, Oliver, Viding, Salekin, & Maughan, 2011; Levenston, Patrick, Bradley, & Lang, 2000).

Additional support for links between low fearful inhibition early in life, callous-unemotional traits, and severe conduct problems comes from neuroimaging studies. Relative to controls, boys with conduct problems and callous-unemotional traits manifest lower right amygdala activity to fearful faces (Jones, Laurens, Herba, Barker, & Viding, 2009). Differential amygdala activation may provide an explanation for three characteristics of psychopathy: poor fear recognition, diminished conditioned fear responses, and deficits in reversal learning (Moul & Dadds, 2013). Finally, adolescent boys with conduct problems and low trait anxiety exhibit greater structural compromises in mesolimbic, septo-hippocampal, and anterior cingulate brain regions than do those with conduct problems and normal levels of anxiety (Sauder et al., 2012).

Low Effortful Control

A third pathway from early temperament to externalizing behaviors is related to deficiencies in effortful control. As outlined earlier, effortful control refers to a child's ability to deploy attentional resources to inhibit prepotent responses in order to regulate behaviors and emotions (Rothbart, 2007). Temperamental dimensions of attentional shifting, focusing, and inhibitory control are critical components of effortful control (Rothbart, Ziaie, & O'Boyle, 1992).

Significant evidence links low effortful control to risk for ADHD-related behaviors (Lemery, Essex, & Smider, 2002). Such findings are consistent with neuropsychological deficits in executive inhibitory control among many children and adolescents with ADHD (Barkley, 1997). In adults, Nigg and colleagues (Nigg, Blaskey, Huang-Pollock, & John, 2002a; Nigg et al., 2002b) found that low conscientiousness (a dimension of personality linked conceptually to low effortful control) was associated with inattention symptoms, whereas hyperactive and impulsive symptoms were related to low agreeableness and high negative emotionality (two additional dimensions of personality). Observational data collected from children between infancy and first grade indicate that ADHD is associated with low effortful control, high anger, and hostile behavior (Nigg, Goldsmith, & Sachek, 2004). In the context of ADHD, comorbid ODD and CD should be addressed to understand the heterogeneity of temperament associations. For instance, associations between negative affect and ADHD could be attributed to comorbid oppositional defiant problems, whereas findings of low anxiety and low physiological arousal (i.e., low fearfulness) may reflect co-occurrence of conduct problems and callous-unemotional traits among those with ADHD (Raine, 2002).

In summary, there are at least three possible pathways from temperamental vulnerability to externalizing behavior. The first involves emotional regulation processes and encompasses traits such as negative emotionality and difficult temperament. Children who present with high negative reactivity and strong reactions to frustration and anger are at increased risk for ODD, nonpsychopathic CD, and hyperactive/impulsive ADHD symptoms. A second trajectory involves low fearful inhibition (i.e., trait anxiety) and is related closely to callous-unemotional traits and

psychopathic behavior. Low fearful inhibition results in insensitivity to punishment learning and disrupts development of empathy and guilt. Extensive literature describes links between low fear, callous-unemotional traits, psychopathic behavior, and amygdala dysfunction. A third pathway is characterized by low effortful control and is associated particularly with ADHD and impulsivity.

Importantly, although these vulnerabilities may occur in isolation, they frequently co-occur. It is not unusual, for example, for children who are high in negative affectivity to also exhibit low effortful control (indeed, these mechanisms often interact among children with ADHD and comorbid conduct problems who show poor emotion regulation; see Beauchaine et al., 2007). Foley and colleagues (2008) found that children with ADHD showed significantly elevated scores on negative reactivity, activity, and impulsivity. Furthermore, recent developments identify a dual-process model whereby both a low-fear temperament (callousness, lack of remorse or guilty) and deficient inhibitory control (impulsivity, poor behavioral control, proneness to boredom) are equally important for the emergence of psychopathy among adults (Fowles & Dindo, 2009). These results indicate that although certain facets of temperament are associated with vulnerability to specific disorders, considerable overlap exists.

Temperament and Psychopathology: End of a Spectrum and/or Vulnerability?

As noted earlier, it is important to consider whether externalizing psychopathology reflects an extreme along a temperamental continuum. Some argue that only severity distinguishes temperament from disorder for any given behavior. For example, attention is often viewed as a quantitative trait that becomes disordered, as in ADHD, when expressed after crossing an arbitrary threshold. Indeed, similarities between symptoms of inattention and the temperamental dimension of effortful control suggest a continuum (De Pauw & Mervielde, 2010). In contrast, cognitive and motor deficits characteristic of ADHD are not typically considered components of temperament (Barkley, 1997). Studies conducted with adults show that personality traits explain about half the variation in ADHD symptoms (Nigg et al., 2002b). Mixed results on continuities between temperament and mental disorders prevent definitive conclusions (Rettew, 2013).

In addition, associations between temperament and psychopathology are likely to vary by disorder. A consensus is that temperament may not be enough to explain the complexity of psychopathology, although some traits share phenotypic resemblance with disorders (Rettew, 2013). A large body of evidence shows that temperament interacts with environmental factors, moderating trajectories to psychopathology (see Pathways to Externalizing Behavior above, Muris & Ollendick, 2005). Interactions between temperamental traits and environmental factors—and interactions among temperamental traits—are complex. The vulnerabilities in question are dimensions of temperament that may not be related directly to core features of externalizing behavior. Nevertheless, when temperamental predispositions interact with adverse social environments, externalizing behaviors may result for some individuals. Here, we detail potential moderators underlying pathways from temperament to psychopathology.

Genetic and Environmental Influences on Trajectories of Psychopathology

Factors that influence temperament and child psychopathology include direct effect of genes, environmental moderation of genetic effects ($G \times E$), and indirect effects of genes through environment (rGE ; Lemery-Chalfant et al., 2013).

Direct Effects of Heritability and Genes

Studies that address heritable associations between temperament and behavioral disorders provide considerable evidence of direct effects. For example, Gjone and Stevenson (1997) showed that a common genetic factor accounted for associations between negative affectivity and both attention problems and aggression 2 years later among 7- to 12-year-olds. Similarly, the proportion of covariance between negative emotionality and oppositional defiant and conduct disorder symptoms that was attributable to heritability accounted for 30% and 50% of the variance in symptoms, respectively (Singh & Waldman, 2010). In a separate twin study spanning infancy to early childhood, shared heritable influences accounted for much of the covariance between negative emotionality and externalizing problems (Schmitz et al., 1999). Thus, specific heritable factors appear to influence both temperament and externalizing behavior.

Furthermore, molecular genetics research has begun to identify specific genes that influence both individual differences in temperament and vulnerability to psychopathology. For example, the 7-repeat allele of the dopamine D₄ receptor gene (DRD4) is associated with individual differences in infant attention (Auerbach, Benjamin, Faroy, Geller, & Ebstein, 2001), mother-reported aggression at age 4 (Schmidt, Fox, Rubin, Hu, & Hamer, 2002), and vulnerability to ADHD (Faraone et al., 2005). Thus, even though temperament represents a set of complex, multifactorial inherited traits, the effects of some specific genes are beginning to be elucidated.

G×E Models

G×E models assume that effects of the environment on developmental outcomes depend on the exposed genotype. When G×E is operative, individuals do not choose environments (Plomin et al., 1977). Rather, their genetic vulnerability renders them susceptible to the environment in which they find themselves. Findings demonstrate consistently that temperament interacts with environmental risk factors to influence later psychopathological outcomes. For example, Crockenberg and Leerkes (2005) reported an association between long hours in nonparental care and externalizing problems 2 years later among infants who were easily frustrated at 6 months. Similarly, Schermerhorn et al. (2013) found that children with temperament profiles including high levels of resistance to control and unadaptability were vulnerable to externalizing problems in the face of chronic family stress. Moreover, negative mothering in the second and third years of life is associated with externalizing problems only among highly negative infants (Belsky, Hsieh, & Crnic, 1998), and maternal sensitivity predicts lower externalizing problems from 2 to 4 years only among children characterized by adverse temperaments (Mesman et al., 2009).

Emerging molecular genetics research has begun to identify specific genes that influence both individual differences in temperament and sensitivity to the environment in predicting behavior. For example, Sheese and colleagues (2007) reported that 18- to 21-month-old children with the DRD₄ 7-repeat allele who experienced low-quality parenting were more likely to exhibit high levels of sensation seeking than were children without the 7-repeat allele who also experienced such parenting. Similarly, Bakermans-Kranenburg and van Ijzendoorn (2006) reported an association between maternal insensitivity and externalizing behaviors, but only for children with the DRD4 7-repeat polymorphism.

rGE Models

rGE describes processes through which an individual's genotype is associated with environmental risk exposures (Knafo & Jaffee, 2013). rGE has gained attention in the developmental psychopathology literature and emphasizes the importance of both (a) mutual influences of genes and environment on behavior and (b) how individuals sometime modulate their environments, either through selection of specific contexts such as deviant peers (active rGE), elicitation of aversive reactions from others (evocative rGE), or when genetic factors that are common to both children and their parents shape the home environment (passive rGE; see Beauchaine & Gatzke-Kopp, 2013; Plomin, 2013). An important example of rGE concerns effects of parenting styles on temperament and behavior (De Clercq, Van Leeuwen, De Fruyt, Van Hiel, & Mervielde, 2008; Rothbaum & Weisz, 1994). For example, previous literature demonstrates that temperamental traits evoke different parenting responses (Lemery-Chalfant et al., 2013). In a retrospective adoption study, Riggins-Caspers et al. (2003) demonstrated that children of biological parents with psychopathology were more likely than those without to experience adoptive parental harsh discipline; these children had more behavior problems as well. Similarly, mothers of irritable infants differ from those of nonirritable infants in both amount and growth trajectory of visual contact, affective stimulation, physical contact, soothing, noninvolvement, and responsiveness to positive signals. Maternal behavior is systematically more positive toward nonirritable compared to irritable infants (van den Bloom & Hoeksma, 1994).

rGE is observed for internalizing behaviors as well. Behavioral inhibition evokes parental overprotection, which then potentiates maladaptive parent-child interactions over time, thus exacerbating the child's fear of novelty and predisposing anxiety symptoms (Kagan & Snidman, 1999). With the exception of genetic associations with substance use, molecular genetic literature on rGE is sparse (Jaffee & Price, 2007). Burt (2009) conducted a study in 132 men who participated in several group activities in the lab and were later asked to judge how much they liked the other members. Men who were heterozygous or homozygous for the G allele of the G1438A polymorphism of the serotonin transporter receptor 2A (5HT2A) gene engaged in more rule-breaking behaviors and were better-

liked by their peers than were men homozygous for A allele. The association between the G1438A polymorphism and peer relationships was mediated in part by its effects on men's rule-breaking behavior. These results represent evidence that genes predispose individuals not only to particular behaviors, but also to the social consequences of those behaviors.

Conclusion

Temperamental traits are biologically based early-developing behavioral and emotional tendencies that are manifested particularly in social interactions and are relatively stable over time and across situations. These characteristics have implications for later development and for vulnerability to psychiatric disorders. Although a consensus regarding the structure of temperament is still lacking, a hierarchical framework seems plausible. This framework suggests a dynamic interplay of approach/withdrawal systems (high-order factors) and reactive/effortful controls (low-order factors) that leads to different temperamental traits.

At least three temperamental trajectories appear to be associated with externalizing behaviors. The first involves emotion regulation processes and encompasses traits such as negative reactivity, emotionality, and temperamental difficulty. Children who present with strong reactions to frustration and anger are at increased risk for hyperactive/impulsive ADHD, ODD, and nonpsychopathic CD. A second trajectory involves low fearful inhibition (anxiety) and is closely related to callous-unemotional traits and psychopathic behavior. Low fearful inhibition interferes with punishment learning, resulting in lack of empathy and guilt. A third pathway is characterized by low effortful control and is associated with ADHD. However, one should not interpret such pathways as being orthogonal; indeed, such traits frequently overlap.

Future Directions

In the past several decades, we have witnessed enormous improvements in our understanding of temperament and its potential links to externalizing behaviors. However, several challenges remain. First, the specificity of temperamental pathways remains unclear. As we have seen, temperamental traits are better predictors of broad vulnerability to externalizing problems than of specific disorders. Second, although the neural substrates of temperament are well understood, much work remains to clarify how trajectories of brain development map onto temperamental stability and change. Some disorders are conceptualized as delays in brain maturation (Shaw et al., 2007), and it will therefore be interesting to know how brain maturation affects intra- and interindividual variation in temperament. Third, assessing temperamental traits in early life appears to have important clinical and public health potential (Rapee, 2013); targeting behavior inhibition may reduce rates of internalizing disorders. It would be tempting to design similar low-risk interventions for temperamental traits to test outcomes in externalizing disorders.

References

- Aebi, M., Plattner, B., Metzke, C. W., Bessler, C., & Steinhausen, H. C. (2013). Parent- and self-reported dimensions of oppositionality in youth: Construct validity, concurrent validity, and the prediction of criminal outcomes in adulthood. *Journal of Child Psychology and Psychiatry*, 54, 941–949.
- Angold, A., Costello, E. J., & Erkanli, A. (1999). Comorbidity. *Journal of Child Psychology and Psychiatry*, 40, 57–87.
- Auerbach, J. G., Benjamin, J., Faroy, M., Geller, V., & Ebstein, R. (2001). DRD4 related to infant attention and information processing: A developmental link to ADHD? *Psychiatric Genetics*, 11, 31–35.
- Bakermans-Kranenburg, M. J., & van Ijzendoorn, M. H. (2006). Gene-environment interaction of the dopamine D4 receptor (DRD4) and observed maternal insensitivity predicting externalizing behavior in preschoolers. *Developmental Psychobiology*, 48, 406–409.
- Barker, E. D., Oliver, B. R., Viding, E., Salekin, R. T., & Maughan, B. (2011). The impact of prenatal maternal risk, fearless temperament and early parenting on adolescent callous-unemotional traits: A 14-year longitudinal investigation. *Journal of Child Psychology and Psychiatry*, 52, 878–888.

- Barkley, R. A. (1997). Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. *Psychological Bulletin*, 121, 65–94.
- Barry, C. T., Frick, P. J., DeShazo, T. M., McCoy, M. G., Ellis, M., & Loney, B. R. (2000). The importance of callous-unemotional traits for extending the concept of psychopathy to children. *Journal of Abnormal Psychology*, 109, 335–340.
- Baumrind, D. (1993). The average expectable environment is not good enough: A response to scarr. *Child Development*, 64, 1299–1317.
- Beauchaine, T. P., Gatzke-Kopp, L., & Mead, H. K. (2007). Polyvagal theory and developmental psychopathology: Emotion dysregulation and conduct problems from preschool to adolescence. *Biological Psychology*, 74, 174–184.
- Beauchaine, T. P., & Gatzke-Kopp, L. M. (2013). Genetic and environmental influences on behavior. In T. P. Beauchaine & S. P. Hinshaw (Eds.), *Child and adolescent psychopathology* (2nd ed., pp. 111–140). Hoboken, NJ: Wiley.
- Beauchaine, T. P., Neuhaus, E., Zalewski, M., Crowell, S. E., & Potapova, N. (2011). Effects of allostatic load on neural systems subserving motivation, mood regulation, and social affiliation. *Development and Psychopathology*, 23, 975–999.
- Belsky, J., Hsieh, K. H., & Crnic, K. (1998). Mothering, fathering, and infant negativity as antecedents of boys' externalizing problems and inhibition at age 3 years: Differential susceptibility to rearing experience? *Development and Psychopathology*, 10, 301–319.
- Bergen, S. E., Gardner, C. O., & Kendler, K. S. (2007). Age-related changes in heritability of behavioral phenotypes over adolescence and young adulthood: A meta-analysis. *Twin Research and Human Genetics*, 10, 423–433.
- Blackson, T. C., Tarter, R. E., Martin, C. S., & Moss, H. B. (1994). Temperament-induced father-son family dysfunction: Etiological implications for child behavior problems and substance abuse. *American Journal of Orthopsychiatry*, 64, 280–292.
- Braungart, J. M., Plomin, R., DeFries, J. C., & Fulker, D. W. (1992). Genetic influence on tester-rated infant temperament as assessed by Bayley's infant behavior record: Nonadoptive and adoptive siblings and twins. *Developmental Psychology*, 28, 40–47.
- Bridges, K. M. B. (1932). Emotional development in early infancy. *Child Development*, 3, 324–341.
- Burke, J. D., Waldman, I., & Lahey, B. B. (2010). Predictive validity of childhood oppositional defiant disorder and conduct disorder: Implications for the *DSM-5*. *Journal of Abnormal Psychology*, 119, 739–751.
- Burt, A. (2009). A mechanistic explanation of popularity: Genes, rule breaking, and evocative gene-environment correlations. *Journal of Personality and Social Psychology*, 96, 783–794.
- Buss, A. H., & Plomin, R. (1975). *A temperament theory of personality development*. New York: Wiley.
- Buss, A. H., & Plomin, R. (1984). *Temperament: Early developing personality traits*. Hillsdale, NJ: Erlbaum.
- Carver, C. S., & Harmon-Jones, E. (2009). Anger is an approach-related affect: Evidence and implications. *Psychological Bulletin*, 135, 183–204.
- Caspi, A., & Silva, P. A. (1995). Temperamental qualities at age three predict personality traits in young adulthood: Longitudinal evidence from a birth cohort. *Child Development*, 66, 486–498.
- Chess, S., & Thomas, A. (1966). *Temperament: Theory and practice*. New York: World Books.
- Chorpita, B. F., Plummer, C. M., & Moffitt, C. E. (2000). Relations of tripartite dimensions of emotion to childhood anxiety and mood disorders. *Journal of Abnormal Child Psychology*, 28, 299–310.
- Cicchetti, D. (2008). A multiple-levels-of-analysis perspective on research in developmental psychopathology. In T.

- P. Beauchaine & S. P. Hinshaw (Eds.), *Child and adolescent psychopathology* (pp. 27–57). Hoboken, NJ: Wiley.
- Cloninger, C. R. (1987). A systematic method for clinical description and classification of personality variants. A proposal. *Archives of General Psychiatry*, 44, 573–588.
- Cloninger, C. R. (2004). *Felling good: The science of well-being*. New York: Oxford University Press.
- Crockenberg, S. C., & Leerkes, E. M. (2005). Infant temperament moderates associations between childcare type and quantity and externalizing and internalizing behaviors at 2-1/2 years. *Infant Behavior and Development*, 28, 20–35.
- Cyphers, L. H., Phillips, K., Fulker, D. W., & Mrazek, D. A. (1990). Twin temperament during the transition from infancy to early childhood. *Journal of the American Academy of Child and Adolescent Psychiatry*, 29, 392–397.
- De Clercq, B., Van Leeuwen, K., De Fruyt, F., Van Hiel, A., & Mervielde, I. (2008). Maladaptive personality traits and psychopathology in childhood and adolescence: The moderating effect of parenting. *Journal of Personality*, 76, 357–383.
- De Pauw, S. S., & Mervielde, I. (2010). Temperament, personality and developmental psychopathology: A review based on the conceptual dimensions underlying childhood traits. *Child Psychiatry and Human Development*, 41, 313–329.
- Digman, J. M. (1990). Personality structure: Emergence of the five-factor model. *Annual Review of Psychology*, 41, 417–440.
- Dumas, J. E., Nissley, J., Nordstrom, A., Smith, E. P., Prinz, R. J., & Levine, D. W. (2005). Home chaos: Sociodemographic, parenting, interactional, and child correlates. *Journal of Clinical Child and Adolescent Psychology*, 34, 93–104.
- Eisenberg, N., Cumberland, A., Spinrad, T. L., Fabes, R. A., Shepard, S. A., Reiser, M.,.... Guthrie, I. K. (2001). The relations of regulation and emotionality to children's externalizing and internalizing problem behavior. *Child Development*, 72, 1112–1134.
- Eisenberg, N., & Spinrad, T. L. (2004). Emotion-related regulation: Sharpening the definition. *Child Development*, 75, 334–339.
- Else-Quest, N. M., Hyde, J. S., Goldsmith, H. H., & Van Hulle, C. A. (2006). Gender differences in temperament: A meta-analysis. *Psychological Bulletin*, 132, 33–72.
- Faraone, S. V., Perlis, R. H., Doyle, A. E., Smoller, J. W., Goralnick, J. J., Holmgren, M. A., & Sklar, P. (2005). Molecular genetics of ADHD. *Biological Psychiatry*, 57, 1313–1323.
- Foley, M., McClowry, S. G., & Castellanos, F. X. (2008). The relationship between ADHD and child temperament. *Journal of Applied Developmental Psychology*, 29, 157–169.
- Fowles, D. C., & Dindo, L. (2009). Temperament and psychopathy: A dual-pathway model. *Current Directions in Psychological Science*, 18, 179–183.
- Frick, P. J. (2004). Integrating research on temperament and childhood psychopathology: Its pitfalls and promise. *Journal of Clinical Child and Adolescent Psychology*, 33, 2–7.
- Frick, P. J., & Morris, A. S. (2004). Temperament and developmental pathways to conduct problems. *Journal of Clinical Child and Adolescent Psychology*, 33, 54–68.
- Frick, P. J., Ray, J. V., Thornton, L. C., & Kahn, R. E. (2014). Can callous-unemotional traits enhance the understanding, diagnosis, and treatment of serious conduct problems in children and adolescents? A comprehensive review. *Psychological Bulletin*, 140, 1–57.
- Gao, Y., Raine, A., Venables, P. H., Dawson, M. E., & Mednick, S. A. (2010). Association of poor childhood fear conditioning and adult crime. *American Journal of Psychiatry*, 167, 56–60.

- Giancola, P. R., Mezzich, A. C., & Tarter, R. E. (1998). Executive cognitive functioning, temperament, and antisocial behavior in conduct-disordered adolescent females. *Journal of Abnormal Psychology, 107*, 629–641.
- Gjone, H., & Stevenson, J. (1997). A longitudinal twin study of temperament and behavior problems: Common genetic or environmental influences? *Journal of the American Academy of Child and Adolescent Psychiatry, 36*, 1448–1456.
- Goldsmith, H. H., Buss, K. A., & Lemery, K. S. (1997). Toddler and childhood temperament: Expanded content, stronger genetic evidence, new evidence for the importance of environment. *Developmental Psychology, 33*, 891–905.
- Goldsmith, H. H., Buss, A. H., Plomin, R., Rothbart, M. K., Thomas, A., Chess, S.,..... McCall, R. B. (1987). Roundtable: What is temperament? Four approaches. *Child Development, 58*, 505–529.
- Goldsmith, H. H., Lemery, K. S., Buss, K. A., & Campos, J. J. (1999). Genetic analyses of focal aspects of infant temperament. *Developmental Psychology, 35*, 972–985.
- Hicks, B. M., Krueger, R. F., Iacono, W. G., McGue, M., & Patrick, C. J. (2004). Family transmission and heritability of externalizing disorders: A twin-family study. *Archives of General Psychiatry, 61*, 922–928.
- Hirshfeld-Becker, D. R., Biederman, J., Faraone, S. V., Violette, H., Wrightsman, J., & Rosenbaum, J. F. (2002). Temperamental correlates of disruptive behavior disorders in young children: Preliminary findings. *Biological Psychiatry, 51*, 563–574.
- Hoeksma, J. B., Oosterlaan, J., & Schipper, E. M. (2004). Emotion regulation and the dynamics of feelings: A conceptual and methodological framework. *Child Development, 75*, 354–360.
- Hoyle, R. H. (2000). Personality processes and problem behavior. *Journal of Personality, 68*, 953–966.
- Hubbard, J. A., Smithmyer, C. M., Ramsden, S. R., Parker, E. H., Flanagan, K. D., Dearing, K. F.,..... Simons, R. F. (2002). Observational, physiological, and self-report measures of children's anger: Relations to reactive versus proactive aggression. *Child Development, 73*, 1101–1118.
- Jaffee, S. R., & Price, T. S. (2007). Gene-environment correlations: A review of the evidence and implications for prevention of mental illness. *Molecular Psychiatry, 12*, 432–442.
- Jensen, P. S., Mrazek, D., Knapp, P. K., Steinberg, L., Pfeffer, C., Schowalter, J., & Shapiro, T. (1997). Evolution and revolution in child psychiatry: ADHD as a disorder of adaptation. *Journal of the American Academy of Child and Adolescent Psychiatry, 36*, 1672–1679.
- Jones, A. P., Laurens, K. R., Herba, C. M., Barker, G. J., & Viding, E. (2009). Amygdala hypoactivity to fearful faces in boys with conduct problems and callous-unemotional traits. *American Journal of Psychiatry, 166*, 95–102.
- Jones, A., & Smith, B. (this volume). Molecular genetics of the externalizing spectrum. In T. P. Beauchaine & S. P. Hinshaw (Eds.) *The oxford handbook of externalizing spectrum disorders*. New York: Oxford University Press.
- Kagan, J. (2013). Behavioral inhibition as a temperamental vulnerability to psychopathology In T. P. Beauchaine & S. P. Hinshaw (Eds.) *Child and adolescent psychopathology* (2nd ed., pp. 227–250). Hoboken, NJ: Wiley.
- Kagan, J., Reznick, J. S., & Snidman, N. (1987). The physiology and psychology of behavioral inhibition in children. *Child Development, 58*, 1459–1473.
- Kagan, J., & Snidman, N. (1999). Early childhood predictors of adult anxiety disorders. *Biological Psychiatry, 46*, 1536–1541.
- Keenan, K., Shaw, D., Delliquadri, E., Giovannelli, J., & Walsh, B. (1998). Evidence for the continuity of early problem behaviors: Application of a developmental model. *Journal of Abnormal Child Psychology, 26*, 441–452.
- Kingston, L., & Prior, M. (1995). The development of patterns of stable, transient, and school-age onset aggressive behavior in young children. *Journal of the American Academy of Child and Adolescent Psychiatry, 34*, 348–358.

- Knafo, A., & Jaffee, S. R. (2013). Gene-environment correlation in developmental psychopathology. *Development and Psychopathology*, 25, 1–6.
- Kochanska, G. (1997). Multiple pathways to conscience for children with different temperaments: From toddlerhood to age 5. *Developmental Psychology*, 33, 228–240.
- Kochanska, G., Barry, R. A., Jimenez, N. B., Hollatz, A. L., & Woodard, J. (2009). Guilt and effortful control: Two mechanisms that prevent disruptive developmental trajectories. *Journal of Personality and Social Psychology*, 97, 322–333.
- Krieger, F. V., Leibenluft, E., Stringaris, A., & Polanczyk, G. V. (2013a). Irritability in children and adolescents: Past concepts, current debates, and future opportunities. *Revista Brasileira de Psiquiatria*, 35, S32–39.
- Krieger, F. V., Polanczyk, V. G., Robert, G., Rohde, L. A., Graeff-Martins, A. S., Salum, G.,.... Stringaris, A. (2013b). Dimensions of oppositionality in a Brazilian community sample: Testing the *DSM-5* proposal and etiological links. *Journal of the American Academy of Child and Adolescent Psychiatry*, 52, 389–400.
- Lahey, B. B. (2004). Commentary: Role of temperament in developmental models of psychopathology. *Journal of Clinical Child and Adolescent Psychology*, 33, 88–93.
- Leibenluft, E., Blair, R. J., Charney, D. S., & Pine, D. S. (2003). Irritability in pediatric mania and other childhood psychopathology. *Annals of the New York Academy of Sciences*, 1008, 201–218.
- Lemery, K. S., Essex, M. J., & Smider, N. A. (2002). Revealing the relation between temperament and behavior problem symptoms by eliminating measurement confounding: Expert ratings and factor analyses. *Child Development*, 73, 867–882.
- Lemery, K. S., Goldsmith, H. H., Klinnert, M. D., & Mrazek, D. A. (1999). Developmental models of infant and childhood temperament. *Developmental Psychology*, 35, 189–204.
- Lemery-Chalfant, K., Kao, K., Swann, G., & Goldsmith, H. H. (2013). Childhood temperament: Passive gene-environment correlation, gene-environment interaction, and the hidden importance of the family environment. *Development and Psychopathology*, 25, 51–63.
- Lengua, L. J., & Wachs, T. D. (2012). Temperament and risk: Resilient and vulnerable responses to adversity. In M. Zentner & R. L. Shiner (Eds.), *Handbook of temperament* (pp. 519–540). New York: Guilford.
- Lengua, L. J., West, S. G., & Sandler, I. N. (1998). Temperament as a predictor of symptomatology in children: Addressing contamination of measures. *Child Development*, 69, 164–181.
- Levenston, G. K., Patrick, C. J., Bradley, M. M., & Lang, P. J. (2000). The psychopath as observer: Emotion and attention in picture processing. *Journal of Abnormal Psychology*, 109, 373–385.
- Leventhal, T., & Brooks-Gunn, J. (2000). The neighborhoods they live in: The effects of neighborhood residence on child and adolescent outcomes. *Psychological Bulletin*, 126, 309–337.
- Loney, B. R., Frick, P. J., Clements, C. B., Ellis, M. L., & Kerlin, K. (2003). Callous-unemotional traits, impulsivity, and emotional processing in adolescents with antisocial behavior problems. *Journal of Clinical Child and Adolescent Psychology*, 32, 66–80.
- Lynam, D. R., Caspi, A., Moffitt, T. E., Wikstrom, P. O., Loeber, R., & Novak, S. (2000). The interaction between impulsivity and neighborhood context on offending: The effects of impulsivity are stronger in poorer neighborhoods. *Journal of Abnormal Psychology*, 109, 563–574.
- Matheny, A. P., Jr. (1980). Bayley's infant behavior record: Behavioral components and twin analyses. *Child Development*, 51, 1157–1167.
- Mesman, J., Stoel, R., Bakermans-Kranenburg, M. J., van IJzendoorn, M. H., Juffer, F., Koot, H. M., & Alink, L. R. (2009). Predicting growth curves of early childhood externalizing problems: Differential susceptibility of children with difficult temperament. *Journal of Abnormal Child Psychology*, 37, 625–636.

- Moul, C., & Dadds, M. R. (2013). Learning-style bias and the development of psychopathy. *Journal of Personality Disorders, 27*, 85–98.
- Muris, P., & Ollendick, T. H. (2005). The role of temperament in the etiology of child psychopathology. *Clinical Child and Family Psychology Review, 8*, 271–289.
- Newman, J. P., Patterson, C. M., & Kosson, D. S. (1987). Response perseveration in psychopaths. *Journal of Abnormal Psychology, 96*, 145–148.
- Nigg, J., Blaskey, L., Huang-Pollock, C., & John, O. (2002a). ADHD symptoms and personality traits: Is ADHD an extreme personality trait? *ADHD Report, 10*, 6–11.
- Nigg, J. T. (2006). Temperament and developmental psychopathology. *Journal of Child Psychology and Psychiatry, 47*, 395–422.
- Nigg, J. T., Goldsmith, H. H., & Sachek, J. (2004). Temperament and ADHD: The development of a multiple pathway model. *Journal of Clinical Child and Adolescent Psychology, 33*, 42–53.
- Nigg, J. T., John, O. P., Blaskey, L. G., Huang-Pollock, C. L., Willcutt, E. G., Hinshaw, S. P., & Pennington, B. (2002b). Big Five dimensions and ADHD symptoms: Links between personality traits and clinical symptoms. *Journal of Personality and Social Psychology, 83*, 451–469.
- Owens, E. B., Shaw, D. S., & Vondra, J. I. (1998). Relations between infant irritability and maternal responsiveness in low-income families. *Infant Behavior and Development, 21*, 761–777.
- Plomin, R. (2013). Commentary: Missing heritability, polygenic scores, and gene-environment correlation. *Journal of Child Psychology and Psychiatry, 54*, 1147–1149.
- Plomin, R., DeFries, J. C., & Loehlin, J. C. (1977). Genotype-environment interaction and correlation in the analysis of human behavior. *Psychological Bulletin, 84*, 309–322.
- Plomin, R., DeFries, J. C., & McClearn, G. E. (2001). *Behavioral genetics* (4th ed.). New York: Worth Publishing.
- Plomin, R., Emde, R. N., Braungart, J. M., Campos, J., Corley, R., Fulker, D. W.,..... DeFries, J. C. (1993). Genetic change and continuity from 14 to 20 months: The MacArthur Longitudinal Twin Study. *Child Development, 64*, 1354–1376.
- Raine, A. (2002). Biosocial studies of antisocial and violent behavior in children and adults: A review. *Journal of Abnormal Child Psychology, 30*, 311–326.
- Rapee, R. M. (2013). The preventative effects of a brief, early intervention for preschool-aged children at risk for internalising: Follow-up into middle adolescence. *Journal of Child Psychology and Psychiatry, 54*, 780–788.
- Rettew, D. (2013). *Child temperament: New thinking about the boundary between traits and illness*. New York: Norton.
- Rettew, D. C., Copeland, W., Stanger, C., & Hudziak, J. J. (2004). Associations between temperament and *DSM-IV* externalizing disorders in children and adolescents. *Journal of Developmental and Behavioral Pediatrics, 25*, 383–391.
- Riese, M. L. (1990). Neonatal temperament in monozygotic and dizygotic twin pairs. *Child Development, 61*, 1230–1237.
- Riggins-Caspers, K. M., Cadoret, R. J., Knutson, J. F., & Langbehn, D. (2003). Biology-environment interaction and evocative biology-environment correlation: Contributions of harsh discipline and parental psychopathology to problem adolescent behaviors. *Behavior Genetics, 33*, 205–220.
- Rothbart, M. K. (1981). Measurement of temperament in infancy. *Child Development, 52*, 569–578.
- Rothbart, M. K. (2007). Temperament, development, and personality. *Current Directions in Psychological Science, 16*, 145–150.

16, 207–212.

Rothbart, M. K., & Ahadi, S. A. (1994). Temperament and the development of personality. *Journal of Abnormal Psychology, 103*, 55–66.

Rothbart, M. K., Ziaie, H., & O'Boyle, C. G. (1992). Self-regulation and emotion in infancy. In N. Eisenberg & R. A. Fabes (Eds.), *Emotion and its regulation in early development: New directions for child development* (No. 55, pp. 7–23). San Francisco: Jossey-Bass.

Rothbaum, F., & Weisz, J. R. (1994). Parental caregiving and child externalizing behavior in nonclinical samples: A meta-analysis. *Psychological Bulletin, 116*, 55–74.

Rowe, R., Costello, E. J., Angold, A., Copeland, W. E., & Maughan, B. (2010). Developmental pathways in oppositional defiant disorder and conduct disorder. *Journal of Abnormal Psychology, 119*, 726–738.

Rutter, M. (1987). Temperament, personality and personality disorder. *British Journal of Psychiatry, 150*, 443–458.

Sauder, C. L., Beauchaine, T. P., Gatzke-Kopp, L. M., Shannon, K. E., & Aylward, E. (2012). Neuroanatomical correlates of heterotypic comorbidity in externalizing male adolescents. *Journal of Clinical Child and Adolescent Psychology, 41*, 346–352.

Saudino, K. J. (2005). Behavioral genetics and child temperament. *Journal of Developmental and Behavioral Pediatrics, 26*, 214–223.

Saudino, K. J., McGuire, S., Reiss, D., Hetherington, E. M., & Plomin, R. (1995). Parent ratings of EAS temperaments in twins, full siblings, half siblings, and step siblings. *Journal of Personality and Social Psychology, 68*, 723–733.

Scarr, S., & McCartney, K. (1983). How people make their own environments: A theory of genotype→ environment effects. *Child Development, 54*, 424–435.

Schermerhorn, A. C., Bates, J. E., Goodnight, J. A., Lansford, J. E., Dodge, K. A., & Pettit, G. S. (2013). Temperament moderates associations between exposure to stress and children's externalizing problems. *Child Development, 84*, 1579–1593.

Schmidt, L. A., Fox, N. A., Rubin, K. H., Hu, S., & Hamer, D. H. (2002). Molecular genetics of shyness and aggression in preschoolers. *Personality and Individual Differences, 33*, 227–238.

Schmitz, S., Fulker, D. W., Plomin, R., Zahn-Waxler, C., Emde, R. N., & DeFries, J. C. (1999). Temperament and problem behaviour during early childhood. *International Journal of Behavioral Development, 23*, 333–355.

Shaw, D. S., Gilliom, M., Ingoldsby, E. M., & Nagin, D. S. (2003). Trajectories leading to school-age conduct problems. *Developmental Psychology, 39*, 189–200.

Shaw, P., Eckstrand, K., Sharp, W., Blumenthal, J., Lerch, J. P., Greenstein, D.,.... Rapoport, J. L. (2007). Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proceedings of the National Academy of Sciences, 104*, 19649–19654.

Sheese, B. E., Voelker, P. M., Rothbart, M. K., & Posner, M. I. (2007). Parenting quality interacts with genetic variation in dopamine receptor D4 to influence temperament in early childhood. *Development and Psychopathology, 19*, 1039–1046.

Shields, A., & Cicchetti, D. (1998). Reactive aggression among maltreated children: The contributions of attention and emotion dysregulation. *Journal of Clinical Child Psychology, 27*, 381–395.

Shiner, R., & Caspi, A. (2003). Personality differences in childhood and adolescence: Measurement, development, and consequences. *Journal of Child Psychology and Psychiatry, 44*, 2–32.

Singh, A. L., & Waldman, I. D. (2010). The etiology of associations between negative emotionality and childhood externalizing disorders. *Journal of Abnormal Psychology, 119*, 376–388.

- Stevenson, J., & Fielding, J. (1985). Ratings of temperament in families of young twins. *British Journal of Developmental Psychology*, 3, 143–152.
- Stringaris, A., Cohen, P., Pine, D. S., & Leibenluft, E. (2009). Adult outcomes of youth irritability: A 20-year prospective community-based study. *American Journal of Psychiatry*, 166, 1048–1054.
- Stringaris, A., & Goodman, R. (2009a). Longitudinal outcome of youth oppositionality: Irritable, headstrong, and hurtful behaviors have distinctive predictions. *Journal of the American Academy of Child and Adolescent Psychiatry*, 48, 404–412.
- Stringaris, A., & Goodman, R. (2009b). Three dimensions of oppositionality in youth. *Journal of Child Psychology and Psychiatry*, 50, 216–223.
- Stringaris, A., Maughan, B., & Goodman, R. (2010). What's in a disruptive disorder? Temperamental antecedents of oppositional defiant disorder: Findings from the Avon Longitudinal Study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 49, 474–483.
- Stringaris, A., Zavos, H., Leibenluft, E., Maughan, B., & Eley, T. C. (2012). Adolescent irritability: Phenotypic associations and genetic links with depressed mood. *American Journal of Psychiatry*, 169, 47–54.
- Tackett, J. L., Waldman, I. D., Van Hulle, C. A., & Lahey, B. B. (2011). Shared genetic influences on negative emotionality and major depression/conduct disorder comorbidity. *Journal of the American Academy of Child and Adolescent Psychiatry*, 50, 818–827.
- Thomas, A., & Chess, S. (1977). *Temperament and development*. New York: Brunner/Mazel.
- van den Bloom, D. C., & Hoeksma, J. B. (1994). The effect of infant irritability on mother-infant interaction: A growth-curve analysis. *Developmental Psychology*, 30, 581–590.
- Wachs, T. D. (1988). Relevance of physical environment influences for toddler temperament. *Infant Behavior and Development*, 11, 431–445.
- Zentner, M., & Bates, J. E. (2008). Child temperament: An integrative review of concepts, research programs, and measures. *International Journal of Developmental Science*, 2, 7–37.
- Zentner, M., & Shiner, R. L. (2012). *Handbook of temperament*. New York: Guilford.

Notes:

⁽¹⁾ Variance in any behavioral trait that is attributable to heritability is often referred to as “genetic” in the behavioral genetics literature. However, there are many nongenetic sources of heritability (Beauchaine & Gatzke-Kopp, 2013), including stress-induced epigenetic effects that alter fetal neurodevelopment and confer vulnerability to externalizing spectrum disorders (Beauchaine et al., 2011). Thus, we use the term “heritable” instead of “genetic” in this chapter and elsewhere in this volume.

Fernanda Valle Krieger

Fernanda Valle Krieger, University of São Paulo, São Paulo, Brazil

Argyris Stringaris

Argyris Stringaris, Institute of Psychiatry, King's College, London, UK

7. DISCUSSÃO FINAL

Na discussão final desta tese gostaria de enfatizar o fluxo conceitual que naturalmente se deu ao longo do doutorado. Os primeiros resultados influenciaram na concepção do artigo seguinte e assim sucessivamente. Este processo proporcionou um progressivo aprofundamento teórico em relação ao meu objeto de estudo. Parti do pressuposto teórico da irritabilidade como uma categoria diagnóstica e no transcorrer dos estudos fui progressivamente associando o constructo a um traço dimensional inespecífico que predispõe o indivíduo a interações disfuncionais em múltiplos níveis, e que tem como resultado variados desfechos.

O primeiro artigo é uma revisão sobre a classificação diagnóstica da irritabilidade e demonstra claramente como distintas categorias diagnósticas se referem ao mesmo constructo. A inclusão de uma categoria própria para a irritabilidade no DSM-5 foi consequência de uma pressão política, porém com escassas evidências científicas para tanto. É importante frisar que o sistema de saúde americano é baseado na classificação do DSM, e os planos de saúde autorizam o tratamento de pacientes através de um diagnóstico categórico, classificado e validado. O meu entendimento é que este foi o maior motivador para a inclusão do diagnóstico de DMDD em detrimento da dimensão irritável do TOD, que além de sugerir uma perspectiva dimensional, já estava validada como uma representação fidedigna do fenótipo da irritabilidade. A evidência demonstrando que o diagnóstico de DMDD aumenta em até 100 vezes a razão de chances (odds ratio) de TOD concomitante, corrobora a hipótese de que estas categorias representam diferentes versões para o mesmo fenômeno. A justificativa dada pela força tarefa do DSM-5 foi de que o TOD, atribuído historicamente a uma forma leve de transtorno de conduta, seria insuficiente para comunicar a intensidade do prejuízo atribuído à irritabilidade, portanto não justificaria a demanda necessária de recursos para o tratamento destas crianças. Por conseguinte, a saída encontrada para um odds ratio de 100 entre os dois diagnósticos foi a inclusão de um critério hierárquico que exclui o diagnóstico de TOD nos casos de DMDD. Ou seja, o DSM-5 incluiu um diagnóstico que tem por natureza a comorbidade com outros diagnósticos em quase a sua totalidade de casos, e diante disso estabeleceu critérios de prioridade entre eles.

Parece-me que esta situação contraria o movimento científico contemporâneo que tem justamente questionado as altas taxas de comorbidade dos manuais classificatórios(96).

O segundo artigo examinou as dimensões subjacentes ao TOD em uma amostra brasileira, pela primeira vez fora do eixo Estados Unidos-Europa, demonstrando a viabilidade do constructo em populações culturalmente distintas. Inicialmente comparamos os diferentes modelos de separação das dimensões, através de análise fatorial confirmatória. O modelo composto por três dimensões (irritable/headstrong/hurtful) demonstrou o melhor ajuste estatístico, confirmando a divisão adotada pelo DSM-5. Além disso, replicamos achados prévios de associações específicas para cada dimensão, “headstrong” com sintomas de hiperatividade e TDAH, “hurtful” com TC e “irritable” com sintomas emocionais e transtornos depressivos e de ansiedade e descrevemos pela primeira vez a associação da dimensão irritável com história familiar de depressão, o que foi confirmado em estudos posteriores(65). A investigação do melhor modelo de estruturação das dimensões do TOD e a confirmação de associações específicas a cada uma delas, validou a dimensão irritável como uma dimensão distinta. Portanto, a principal contribuição deste estudo foi ratificar a dimensão irritável como uma representação fidedigna do fenótipo da irritabilidade, viabilizando assim a sua mensuração. A irritabilidade não possuía até então um instrumento específico de avaliação, o que obstaculizava o estudo do fenótipo. Atualmente a “Affective Reactivity Index” (ARI) está disponível, mas segue pouco utilizada(97).

A motivação para o artigo 3 partiu da observação sistemática de que a irritabilidade era um denominador comum de diversos transtornos. Após o lançamento do DSM-5 e da constatação de que seu sistema de classificação se mostrava insuficiente diante da complexidade dos processos psicopatológicos, o NIMH lançou o Research Domain Criteria (RDoC), que propôs uma mudança de paradigma no entendimento dos transtornos mentais. O RDoC sugere a investigação da psicopatologia em múltiplos níveis, examinando mecanismos subjacentes às categorias diagnósticas(98). Neste contexto, concomitante a progressiva da irritabilidade como um mecanismo subjacente a vários transtornos, o objetivo do artigo 3 foi investigar a validade preditiva da irritabilidade em diferentes cenários clínicos. A intenção era examinar se a irritabilidade descrita no TDAH era a mesma irritabilidade descrita em indivíduos saudáveis ou a mesma irritabilidade em crianças com transtornos emocionais. A hipótese era de que as

irritabilidades descritas em distintos cenários era o mesmo constructo subjacente. De fato, a hipótese foi confirmada mostrando que a irritabilidade está associada a um aumento do prejuízo funcional independente da categoria observada na “superfície”. Nosso resultados sustentam a hipótese da irritabilidade como um fenótipo inespecífico que predispõe o indivíduo a uma morbidade aumentada e que frequentemente é um precursor de psicopatologia. A semelhança do fenótipo com traços de temperamento caracterizados por prejuízo na regulação emocional não pode ser negligenciada, particularmente porque os desfechos destes diferentes constructos convergem. Temperamentos como “difficult temperament”, “negative affect” e “emotionality”, todos definidos por excessiva reatividade diante de estímulos negativos, estão implicados no processo psicopatológico tanto de transtornos internalizantes quanto externalizantes, assim como a irritabilidade(79, 99, 100, 101).

Diante dessa mudança de paradigma, o quarto artigo surgiu com o objetivo de identificar aspectos etiológicos do fenótipo da irritabilidade, através de mecanismos próximos ao fenótipo. Isso incluiu aspectos como agressividade reativa, emocionalidade, raiva, excessiva reatividade, déficits no controle inibitório e afetividade negativa. O escore poligênico derivado destes aspectos foi altamente preditivo de irritabilidade. Além disso, influências ambientais foram incluídas no modelo sugerindo uma correlação gene ambiente (rGE). Esse achado aproxima o fenótipo da irritabilidade de traços de temperamento. De fato, evidências sugerem que determinadas características de temperamento influenciam a resposta do ambiente. O comportamento das mães de crianças não irritadas é predominantemente positivo e difere significativamente daquele observado em mães cujos filhos apresentam irritabilidade. Mães de bebês irritados demonstraram menor contato visual, menos envolvimento afetivo e acariciador e são menos responsivas a sinais positivos(102). Os resultados deste estudo demonstram que influências genéticas e ambientais estão implicadas na etiologia da irritabilidade e sugere que relações bidirecionais entre estes aspectos determinam diferentes gradientes do fenótipo, que por sua vez predis põem a variados desfechos dentro do processo psicopatológico.

8. CONCLUSÕES

Esta tese conclui que a irritabilidade é um fenótipo que pode ser mensurado através da dimensão irritável do TOD. Entretanto, nossos resultados sugerem que a irritabilidade se trata de um constructo dimensional que subjaz múltiplos cenários e que predispõe um aumento da morbidade e prejuízo funcional ao longo deles. Além disso, através de uma perspectiva dimensional, os distintos gradientes de irritabilidade parecem predispor a trajetórias distintas de desenvolvimento. A parte inferior da curva caracteriza o fenótipo como um precursor inespecífico para psicopatologia, podendo resultar em variados desfechos. A medida que a intensidade aumenta, correlações com fatores ambientais contribuem para a determinação dos desfechos. O extremo superior da curva configura um fenótipo associado a um importante prejuízo funcional e se caracteriza por um alto índice de comorbidades. A discussão acerca da classificação diagnóstica da irritabilidade se refere especificamente ao subgrupo situado no extremo superior da curva. Entretanto, um entendimento mais abrangente do constructo, particularmente a dimensionalidade dele, se faz necessário. A semelhança com traços de temperamento sugerem origens primitivas, que iniciam nos primeiros anos de vida e que a partir das relações com o ambiente podem tornar-se mais ou menos disfuncionais. Neste sentido, a irritabilidade pode ser entendida através do modelo proposto pelo RDoC. No sentido de avançar o conhecimento a seu respeito, é preciso entender a irritabilidade em múltiplos níveis e investigar especificamente quais fatores determinam sua origem, mas também quais mecanismos determinam sua perpetuação e consequente participação no processo psicopatológico ao longo do desenvolvimento.

9. REFERÊNCIAS

1. Krieger FV, Pheula GF, Coelho R, Zeni T, Tramontina S, Zeni CP, Rohde LA. An open-label trial of risperidone in children and adolescents with severe mood dysregulation. *J Child Adolesc Psychopharmacol*. 2011;21:237-43.
2. Salum GA, Gadelha A, Pan PM, Moriyama TS, Graeff-Martins AS, Tamanaha AC, Alvarenga P, Krieger FV, Fleitlich-Bilyk B, Jackowski A, Sato JR, Brietzke E, Polanczyk GV, Brentani H, Mari JD, Do Rosario MC, Manfro GG, Bressan RA, Mercadante MT, Miguel EC, Rohde LA. High risk cohort study for psychiatric disorders in childhood: Rationale, design, methods and preliminary results. *Int J Methods Psychiatr Res*. 2014.
3. Stringaris A, Goodman R. Three dimensions of oppositionality in youth. *J Child Psychol Psychiatry*. 2009;50:216-23.
4. Cichetti D. The emergence of developmental psychopathology. *Child Dev*. 1984;55.
5. Sroufe LA, Rutter M. The domain of developmental psychopathology. *Child Dev*. 1984;55:17-29.
6. Rutter M, Sroufe LA. Developmental psychopathology: Concepts and challenges. *Dev Psychopathol*. 2000;12:265-96.
7. Costello EJ, Foley DL, Angold A. 10-year research update review: The epidemiology of child and adolescent psychiatric disorders: Ii. Developmental epidemiology. *J Am Acad Child Adolesc Psychiatry*. 2006;45:8-25.
8. Costello EJ, Compton SN, Keeler G, Angold A. Relationships between poverty and psychopathology: A natural experiment. *JAMA*. 2003;290:2023-9.
9. Copeland W, Shanahan L, Costello EJ, Angold A. Configurations of common childhood psychosocial risk factors. *J Child Psychol Psychiatry*. 2009;50:451-9.
10. Lynam DR, Caspi A, Moffitt TE, Wikstrom PO, Loeber R, Novak S. The interaction between impulsivity and neighborhood context on offending: The effects of impulsivity are stronger in poorer neighborhoods. *J Abnorm Psychol*. 2000;109:563-74.
11. Springer KW, Sheridan J, Kuo D, Carnes M. Long-term physical and mental health consequences of childhood physical abuse: Results from a large population-based sample of men and women. *Child Abuse & Neglect*. 2007;31:517-30.

12. Sroufe LA. Psychopathology as an outcome of development. *Dev Psychopathol.* 1997;9:251-68.
13. Rutter M. The interplay of nature, nurture, and developmental influences: The challenge ahead for mental health. *Arch Gen Psychiatry.* 2002;59:996-1000.
14. Casey BJ, Oliveri ME, Insel T. A neurodevelopmental perspective on the research domain criteria (rdoc) framework. *Biol Psychiatry.* 2014;76:350-3.
15. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of dsm-iv disorders in the national comorbidity survey replication. *Arch Gen Psychiatry.* 2005;62:593-602.
16. Copeland WE, Shanahan L, Costello EJ, Angold A. Childhood and adolescent psychiatric disorders as predictors of young adult disorders. *Arch Gen Psychiatry.* 2009;66:764-72.
17. Kim-Cohen J, Caspi A, Moffitt TE, Harrington H, Milne BJ, Poulton R. Prior juvenile diagnoses in adults with mental disorder: Developmental follow-back of a prospective-longitudinal cohort. *Arch Gen Psychiatry.* 2003;60:709-17.
18. American Psychiatric Association. *Diagnostic and statistical manual for mental disorders 3rd ed.* Washington, DC: American Psychiatric Association; 1980.
19. American Psychiatric Association P. *Diagnostic and statistical manual for mental disorders 4th ed.* Washington, DC: American Psychiatric Association; 1994.
20. Maughan B, Rowe R, Messer J, Goodman R, Meltzer H. Conduct disorder and oppositional defiant disorder in a national sample: Developmental epidemiology. *J Child Psychol Psychiatry.* 2004;45:609-21.
21. Costello EJ, Mustillo S, Erkanli A, Keeler G, Angold A. Prevalence and development of psychiatric disorders in childhood and adolescence. *Arch Gen Psychiatry.* 2003;60:837-44.
22. Boylan K, Vaillancourt T, Boyle M, Szatmari P. Comorbidity of internalizing disorders in children with oppositional defiant disorder. *Eur Child Adolesc Psychiatry.* 2007;16:484-94.
23. Fleitlich-Bilyk B, Goodman R. Prevalence of child and adolescent psychiatric disorders in southeast brazil. *J Am Acad Child Adolesc Psychiatry.* 2004;43:727-34.
24. Nock MK, Kazdin AE, Hiripi E, Kessler RC. Lifetime prevalence, correlates, and persistence of oppositional defiant disorder: Results from the national comorbidity survey replication. *J Child Psychol Psychiatry.* 2007;48:703-13.

25. Rutter M, Caspi A, Moffitt TE. Using sex differences in psychopathology to study causal mechanisms: Unifying issues and research strategies. *J Child Psychol Psychiatry*. 2003;44:1092-115.
26. Rowe R, Maughan B, Pickles A, Costello EJ, Angold A. The relationship between dsm-iv oppositional defiant disorder and conduct disorder: Findings from the great smoky mountains study. *J Child Psychol Psychiatry*. 2002;43:365-73.
27. Rowe R, Maughan B, Costello EJ, Angold A. Defining oppositional defiant disorder. *J Child Psychol Psychiatry*. 2005;46:1309-16.
28. Rowe R, Costello EJ, Angold A, Copeland WE, Maughan B. Developmental pathways in oppositional defiant disorder and conduct disorder. *J Abnorm Psychol*. 2010;119:726-38.
29. Angold A, Costello EJ. Toward establishing an empirical basis for the diagnosis of oppositional defiant disorder. *J Am Acad Child Adolesc Psychiatry*. 1996;35:1205-12.
30. Burke JD, Waldman I, Lahey BB. Predictive validity of childhood oppositional defiant disorder and conduct disorder: Implications for the dsm-v. *J Abnorm Psychol*. 2010;119:739-51.
31. Althoff RR. Dysregulated children reconsidered. *J Am Acad Child Adolesc Psychiatry*. 2010;49:302-5.
32. Stringaris A, Goodman R. Longitudinal outcome of youth oppositionality: Irritable, headstrong, and hurtful behaviors have distinctive predictions. *J Am Acad Child Adolesc Psychiatry*. 2009;48:404-12.
33. Burke JD, Loeber R. Oppositional defiant disorder and the explanation of the comorbidity between behavioral disorders and depression. *Clinical Psychology: Science and Practice*. 2010;17:319-26.
34. Burke JD, Hipwell AE, Loeber R. Dimensions of oppositional defiant disorder as predictors of depression and conduct disorder in preadolescent girls. *J Am Acad Child Adolesc Psychiatry*. 2010;49:484-92.
35. Ezpeleta L, Granero R, de la Osa N, Penelo E, Domenech JM. Dimensions of oppositional defiant disorder in 3-year-old preschoolers. *J Child Psychol Psychiatry*. 2012.

36. Drabick DA, Gadow KD. Deconstructing oppositional defiant disorder: Clinic-based evidence for an anger/irritability phenotype. *J Am Acad Child Adolesc Psychiatry*. 2012;51:384-93.
37. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders 5th ed*. Washington, DC: American Psychiatric Association; 2013.
38. Harpaz-Rotem I, Leslie DL, Martin A, Rosenheck RA. Changes in child and adolescent inpatient psychiatric admission diagnoses between 1995 and 2000. *Soc Psychiatry Psychiatr Epidemiol*. 2005;40:642-7.
39. Blader JC, Carlson GA. Increased rates of bipolar disorder diagnoses among u.S. Child, adolescent, and adult inpatients, 1996-2004. *Biol Psychiatry*. 2007;62:107-14.
40. Moreno C, Laje G, Blanco C, Jiang H, Schmidt AB, Olfson M. National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. *Arch Gen Psychiatry*. 2007;64:1032-9.
41. Geller B, Luby J. Child and adolescent bipolar disorder: A review of the past 10 years. *J Am Acad Child Adolesc Psychiatry*. 1997;36:1168-76.
42. Geller B, Tillman R, Bolhofner K. Proposed definitions of bipolar i disorder episodes and daily rapid cycling phenomena in preschoolers, school-aged children, adolescents, and adults. *J Child Adolesc Psychopharmacol*. 2007;17:217-22.
43. Biederman J, Klein RG, Pine DS, Klein DF. Resolved: Mania is mistaken for adhd in prepubertal children. *J Am Acad Child Adolesc Psychiatry*. 1998;37:1091-6.
44. Biederman J, Faraone SV, Wozniak J, Mick E, Kwon A, Aleardi M. Further evidence of unique developmental phenotypic correlates of pediatric bipolar disorder: Findings from a large sample of clinically referred preadolescent children assessed over the last 7 years. *J Affect Disord*. 2004;82 Suppl 1:S45-58.
45. Leibenluft E, Blair RJ, Charney DS, Pine DS. Irritability in pediatric mania and other childhood psychopathology. *Ann N Y Acad Sci*. 2003;1008:201-18.
46. Bhangoo RK, Dell ML, Towbin K, Myers FS, Lowe CH, Pine DS, Leibenluft E. Clinical correlates of episodicity in juvenile mania. *J Child Adolesc Psychopharmacol*. 2003;13:507-14.
47. Brotman MA, Kassem L, Reising MM, Guyer AE, Dickstein DP, Rich BA, Towbin KE, Pine DS, McMahon FJ, Leibenluft E. Parental diagnoses in youth with

narrow phenotype bipolar disorder or severe mood dysregulation. *Am J Psychiatry*. 2007;164:1238-41.

48. Leibenluft E. Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. *Am J Psychiatry*. 2011;168:129-42.

49. Roy AK, Klein RG, Angelosante A, Bar-Haim Y, Leibenluft E, Hulvershorn L, Dixon E, Dodds A, Spindel C. Clinical features of young children referred for impairing temper outbursts. *J Child Adolesc Psychopharmacol*. 2013;23:588-96.

50. Leibenluft E, Cohen P, Gorrindo T, Brook JS, Pine DS. Chronic versus episodic irritability in youth: A community-based, longitudinal study of clinical and diagnostic associations. *J Child Adolesc Psychopharmacol*. 2006;16:456-66.

51. Leibenluft E, Charney DS, Towbin KE, Bhangoo RK, Pine DS. Defining clinical phenotypes of juvenile mania. *Am J Psychiatry*. 2003;160:430-7.

52. Deveney CM, Connolly ME, Jenkins SE, Kim P, Fromm SJ, Pine DS, Leibenluft E. Neural recruitment during failed motor inhibition differentiates youths with bipolar disorder and severe mood dysregulation. *Biol Psychol*. 2012;89:148-55.

53. Towbin K, Axelson D, Leibenluft E, Birmaher B. Differentiating bipolar disorder-not otherwise specified and severe mood dysregulation. *J Am Acad Child Adolesc Psychiatry*. 2013;52:466-81.

54. Stringaris A, Baroni A, Haimm C, Brotman M, Lowe CH, Myers F, Rustgi E, Wheeler W, Kayser R, Towbin K, Leibenluft E. Pediatric bipolar disorder versus severe mood dysregulation: Risk for manic episodes on follow-up. *J Am Acad Child Adolesc Psychiatry*. 2010;49:397-405.

55. Brotman MA, Schmajuk M, Rich BA, Dickstein DP, Guyer AE, Costello EJ, Egger HL, Angold A, Pine DS, Leibenluft E. Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. *Biol Psychiatry*. 2006;60:991-7.

56. Stoddard J, Stringaris A, Brotman MA, Montville D, Pine DS, Leibenluft E. Irritability in child and adolescent anxiety disorders. *Depress Anxiety*. 2014;31:566-73.

57. Copeland WE, Angold A, Costello EJ, Egger H. Prevalence, comorbidity, and correlates of dsm-5 proposed disruptive mood dysregulation disorder. *Am J Psychiatry*. 2013;170:173-9.

58. Dougherty LR, Smith VC, Bufferd SJ, Carlson GA, Stringaris A, Leibenluft E, Klein DN. Dsm-5 disruptive mood dysregulation disorder: Correlates and predictors in young children. *Psychol Med*. 2014;1-12.
59. Eisenberg N, Cumberland A, Spinrad TL, Fabes RA, Shepard SA, Reiser M, Murphy BC, Losoya SH, Guthrie IK. The relations of regulation and emotionality to children's externalizing and internalizing problem behavior. *Child Dev*. 2001;72:1112-34.
60. Singh AL, Waldman ID. The etiology of associations between negative emotionality and childhood externalizing disorders. *J Abnorm Psychol*. 2010;119:376-88.
61. Tackett JL, Waldman ID, Van Hulle CA, Lahey BB. Shared genetic influences on negative emotionality and major depression/conduct disorder comorbidity. *J Am Acad Child Adolesc Psychiatry*. 2011;50:818-27.
62. Stringaris A, Maughan B, Goodman R. What's in a disruptive disorder? Temperamental antecedents of oppositional defiant disorder: Findings from the avon longitudinal study. *J Am Acad Child Adolesc Psychiatry*. 2010;49:474-83.
63. Stringaris A, Zavos H, Leibenluft E, Maughan B, Eley TC. Adolescent irritability: Phenotypic associations and genetic links with depressed mood. *Am J Psychiatry*. 2012;169:47-54.
64. Stringaris A, Maughan B, Copeland WS, Costello EJ, Angold A. Irritable mood as a symptom of depression in youth: Prevalence, developmental, and clinical correlates in the great smoky mountains study. *J Am Acad Child Adolesc Psychiatry*. 2013;52:831-40.
65. Wiggins JL, Mitchell C, Stringaris A, Leibenluft E. Developmental trajectories of irritability and bidirectional associations with maternal depression. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2014;53:1191-205.e4.
66. Leibenluft E, Stoddard J. The developmental psychopathology of irritability. *Dev Psychopathol*. 2013;25:1473-87.
67. Berkowitz L. Frustration-aggression hypothesis: Examination and reformulation. *Psychol Bull*. 1989;106:59-73.
68. Bridges KMB. Emotional development in early infancy. *Child Dev*. 1932;3:324-41.

69. Potegal M, Davidson RJ. Temper tantrums in young children: 1. Behavioral composition. *J Dev Behav Pediatr.* 2003;24:140-7.
70. Cote SM, Vaillancourt T, LeBlanc JC, Nagin DS, Tremblay RE. The development of physical aggression from toddlerhood to pre-adolescence: A nation wide longitudinal study of canadian children. *J Abnorm Child Psychol.* 2006;34:71-85.
71. Bell MA, Deater-Deckard K. Biological systems and the development of self-regulation: Integrating behavior, genetics, and psychophysiology. *J Dev Behav Pediatr.* 2007;28:409-20.
72. Wakschlag LS, Choi SW, Carter AS, Hullsiek H, Burns J, McCarthy K, Leibenluft E, Briggs-Gowan MJ. Defining the developmental parameters of temper loss in early childhood: Implications for developmental psychopathology. *J Child Psychol Psychiatry.* 2012;53:1099-108.
73. Hirshfeld-Becker DR, Biederman J, Henin A, Faraone SV, Micco JA, van Grondelle A, Henry B, Rosenbaum JF. Clinical outcomes of laboratory-observed preschool behavioral disinhibition at five-year follow-up. *Biol Psychiatry.* 2007;62:565-72.
74. Guerin DW, Gottfried AW, Thomas CW. Difficult temperament and behaviour problems: A longitudinal study from 1.5 to 12 years. *International Journal of Behavioral Development.* 1997;21:71-90.
75. Deater-Deckard K, Petrill SA, Thompson LA. Anger/frustration, task persistence, and conduct problems in childhood: A behavioral genetic analysis. *J Child Psychol Psychiatry.* 2007;48:80-7.
76. Crick NR, Dodge KA. Social information-processing mechanisms in reactive and proactive aggression. *Child Dev.* 1996;67:993-1002.
77. Vitaro F, Brendgen M, Tremblay RE. Reactively and proactively aggressive children: Antecedent and subsequent characteristics. *J Child Psychol Psychiatry.* 2002;43:495-505.
78. Shiner R, Caspi A. Personality differences in childhood and adolescence: Measurement, development, and consequences. *J Child Psychol Psychiatry.* 2003;44:2-32.
79. Mesman J, Stoel R, Bakermans-Kranenburg MJ, van IJzendoorn MH, Juffer F, Koot HM, Alink LR. Predicting growth curves of early childhood externalizing

problems: Differential susceptibility of children with difficult temperament. *J Abnorm Child Psychol.* 2009;37:625-36.

80. Dougherty LR, Smith VC, Bufferd SJ, Stringaris A, Leibenluft E, Carlson GA, Klein DN. Preschool irritability: Longitudinal associations with psychiatric disorders at age 6 and parental psychopathology. *J Am Acad Child Adolesc Psychiatry.* 2013;52:1304-13.

81. Stringaris A, Cohen P, Pine DS, Leibenluft E. Adult outcomes of youth irritability: A 20-year prospective community-based study. *Am J Psychiatry.* 2009;166:1048-54.

82. Siever LJ. Neurobiology of aggression and violence. *Am J Psychiatry.* 2008;165:429-42.

83. Panksepp J, Biven L. *The archeology of mind: Neuroevolutionary origins of humans emotions (1st ed.)*. New York: W.W. Norton & Company; 2012.

84. Blair RJ. Psychopathy, frustration, and reactive aggression: The role of ventromedial prefrontal cortex. *Br J Psychol.* 2010;101:383-99.

85. Damasio AR, Grabowski TJ, Bechara A, Damasio H, Ponto LL, Parvizi J, Hichwa RD. Subcortical and cortical brain activity during the feeling of self-generated emotions. *Nat Neurosci.* 2000;3:1049-56.

86. Ochsner KN, Ray RR, Hughes B, McRae K, Cooper JC, Weber J, Gabrieli JDE, Gross JJ. Bottom-up and top-down processes in emotion generation: Common and distinct neural mechanisms. *Psychol Sci.* 2009;20:1322-31.

87. Rich BA, Brotman MA, Dickstein DP, Mitchell DG, Blair RJ, Leibenluft E. Deficits in attention to emotional stimuli distinguish youth with severe mood dysregulation from youth with bipolar disorder. *J Abnorm Child Psychol.* 2010;38:695-706.

88. Hoeksma JB, Oosterlaan J, Schipper EM. Emotion regulation and the dynamics of feelings: A conceptual and methodological framework. *Child Dev.* 2004;75:354-60.

89. Barkley RA. Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of adhd. *Psychol Bull.* 1997;121:65-94.

90. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. *Annu Rev Neurosci.* 2001;24:167-202.

91. Barkley RA. *Adhd and the nature of self-control*. New York: The Guilford Press; 1997.

92. Gross JJ. Emotion regulation: Affective, cognitive, and social consequences. *Psychophysiology*. 2002;39:281-91.
93. Ochsner KN, Ray RD, Cooper JC, Robertson ER, Chopra S, Gabrieli JDE, Gross JJ. For better or for worse: Neural systems supporting the cognitive down- and up-regulation of negative emotion. *Neuroimage*. 2004;23:483-99.
94. Adleman NE, Kayser R, Dickstein D, Blair RJ, Pine D, Leibenluft E. Neural correlates of reversal learning in severe mood dysregulation and pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry*. 2011;50:1173-85 e2.
95. Dickstein DP, Nelson EE, McClure EB, Grimley ME, Knopf L, Brotman MA, Rich BA, Pine DS, Leibenluft E. Cognitive flexibility in phenotypes of pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;46:341-55.
96. Adam D. Mental health: On the spectrum. *Nature*. 2013;496:416-8.
97. Stringaris A, Goodman R, Ferdinando S, Razdan V, Muhrer E, Leibenluft E, Brotman MA. The affective reactivity index: A concise irritability scale for clinical and research settings. *J Child Psychol Psychiatry*. 2012;53:1109-17.
98. Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: The seven pillars of rdoc. *BMC Med*. 2013;11:126.
99. Muris P, Ollendick TH. The role of temperament in the etiology of child psychopathology. *Clin Child Fam Psychol Rev*. 2005;8:271-89.
100. Frick PJ, Morris AS. Temperament and developmental pathways to conduct problems. *J Clin Child Adolesc Psychol*. 2004;33:54-68.
101. Lengua LJ, West SG, Sandler IN. Temperament as a predictor of symptomatology in children: Addressing contamination of measures. *Child Dev*. 1998;69:164-81.
102. van den Bloom DC, Hoeksma JB. The effect of infant irritability on mother-infant interaction: A growth-curve analysis. *Dev Psychol*. 1994;30:581-90.