UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM PSIQUIATRIA E CIÊNCIAS DO COMPORTAMENTO

TESE DE DOUTORADO

CLASSIFICAÇÃO DIAGNÓSTICA EM PSIQUIATRIA DA INFÂNCIA E ADOLESCÊNCIA: LIMITAÇÕES VIGENTES E MODELOS ALTERNATIVOS GUIADOS PELOS DADOS

Arthur Gus Manfro

Orientador: Giovanni Abrahão Salum

Co-orientador: Luis Augusto Paim Rohde

Porto Alegre, agosto de 2020

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SUMÁRIO

ABREVIATURAS E SIGLAS

ADHD	*Attention Deficit/Hyperacivity Disorder*
AUC	*Area Under the Curve*
BHRCS	*Brazilian High-Risk Cohort Study*
CBCL	*Child Behavior Checklist*
CC	*Community Comparison*
CFA	*Confirmatory Factor Analysis*
CID	Classificação Internacional de Doenças
CL	*Childhood-Limited*
DAWBA	*Development and Well-Being Assessment*
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
EDC	*Executive Dysfunction Class*
EF	*Executive Function*
FE	Funções Executivas
GWAS	*Genome-Wide Association Study*
IQ	*Intelligence Quotient*
LCA	*Latent Class Analysis*
NIMH	*National Institue of Mental Health*
Per	*Persistent*
PGC	*Psychiatric Genomics Consortium*
PRS	*Polygenic Risk Score*
RDoC	*Research Domain Criteria*
ROC	*Receiver Operating Characteristic*
SDQ	*Strengths and Difficulties Questionnaire*
TDAH	Transtorno de Déficit de Atenção/Hiperatividade
YO	*Youth-Onset*

RESUMO

O diagnóstico em psiquiatria é classicamente determinado avaliando a presença de sinais e sintomas, conforme operacionalizado pelos manuais diagnósticos vigentes. Essa abordagem descritivo-fenomenológica é questionada por modelos alternativos da nosologia psiquiátrica, que pretendem construir sistemas de classificação baseados em critérios objetivos, como o Research Domain Criteria (RDoC). Os dois estudos dessa tese inserem-se nesse contexto, objetivando avaliar falhas no sistema classificatório vigente (Estudo #1) e testar a validade de estratégias alternativas de classificação (Estudo #2). Os estudos utilizam como base o Estudo Brasileiro de Alto Risco para Transtornos Psiquiátricos, uma coorte de jovens brasileiros (n=2.511) que integra avaliações clínicas, neuropsicológicas, genéticas e de neuroimagem. O primeiro artigo visou avaliar a presença de casos de Transtorno de Déficit de Atenção/Hiperatividade (TDAH) com início após os 12 anos de idade, desrespeitando a exigência etária do 5º Manual Diagnóstico e Estatístico de Transtornos Mentais (DSM-5). Esse estudo identificou participantes com TDAH de início na adolescência e mostrou que esses jovens, apesar de não terem transtornos mentais antes de incidirem com TDAH, já apresentavam mais sintomas psiquiátricos e pior performance escolar e executiva. Tal resultado leva à hipótese de que o TDAH de início tardio possa ser entendido como uma manifestação da maior psicopatologia de base dos participantes acometidos, por meio de uma continuidade heterotípica. O segundo estudo testou se uma classificação baseada exclusivamente nas funções executivas dos participantes seria capaz de associar-se e de predizer desfechos de interesse clínico e correlatos biológicos. Os resultados mostraram que uma classe de participantes com déficits de funções executivas mostrou,

independentemente de transtornos mentais e da inteligência, maiores dificuldades na vida social, familiar e escolar, diferenças em marcadores genéticos de risco e menores áreas de superfície corticais. Esse estudo demontrou que uma classificação baseada em critérios objetivos pode ser operacionalizada em uma ferramenta de interesse clínico. A tese conclui que adequação de sistemas diagnósticos na psiquiatria deve ser empiricamente testada, de forma que suas limitações e/ou potencialidades possam ser devidamente abordados.

Palavras-Chave: Psiquiatria Infatil; TDAH; Função Executiva; Psicopatologia.

ABSTRACT

Psychatric diagnoses are classicaly determined by evaluating the presence of signs and symptoms, as operationalized by the current diagnostic manuals. This descriptive-phenomenological approach is questioned by alternative models of psychiatry nosology, which aim to develop classificatory systems bases on objetctive criteria, e.g the Research Domain Criteria (RDoC). Both studies of this thesis are inserted in this context, aiming o evaluate flaws in the current classificatory system (Study #1) and test the validity of alternative classification strategies (Study #2). The studies use as base the Brazilian High-Risk Study for Psychiatric Disorders (n=2,511), which integrates clinical, neuropsychological, genetical and neuroimaging evaluations. The first study's goal was to investigate the presence of Attention Deficit/Hyperactivity Disorder (ADHD) with an age of onset after 12 yers old, therefore disrespecting the age-criterion of the 5th Diagnostic and Statistical Manual of Mental Disorders (DSM-5). This study identified participants with youth-onset ADHD e showed that that they, despite noth having prior psychiatric comorbidities before ADHD incidence, already showed more psychiatric symptoms and worse school and executive function performances. The results raise the hypothesis that late-onset ADHD can be understood as a manifestation of the higher base psychopathology of the affected participants, through an heterotypical continuity. The second study testes whether a classification based only on executive functions measures of the participants was capable of associating and predicting clinically relevant outcomes and biological correlates. The results showed that an executive dysfunction class had higher impairment on school, family and social life, differenes on genetic risk markers and lower cortical surface areas, over and above psychiatric disorders and intelligence. This study demonstrated that an objective-based classification may be

operationalized in a clinically useful tool. The thesis concludes that the adequacy of psychiatric diagnostic systems must be empirically tested, so that its limitations and/or potentialities can be properly addressed.

Key-Words: Child Psychiatry; ADHD; Executive Function; Psychopathology.

1. INTRODUÇÃO

1.1. Apresentação

Este trabalho consiste na teste de doutorado intitulada “Classificação Diagnóstica em Psiquiatria da Infância e Adolescência: Limitações Vigentes e Modelos Alternativos Guiados Pelos Dados”, apresentada ao Programa de Pós-Graduação em Psiquiaria e Ciências do Comportamento. O objetivo da tese é testar critérios diagnósticos vigentes da psiquiatria da infância e da adolescência nos manuais classificatórios e explorar outras alternativas para diagnóstico usando paradigmas inovadores guiados pelos dados. A tese é composta de dois estudos.

O primeiro estudo tem como objetivo avaliar o critério de idade de início dos sintomas como critério necessário para o diagnóstico do Transtorno de Déficit de Atenção/Hiperatividade (TDAH). Atualmente, os sintomas devem iniciar antes dos 12 anos de idade para que o indivíduo possa ser propriamente classificado como acometido do transtorno. No entanto, estudos realizados nos últimos 5 anos desafiaram este paradigma mostrando que em estudos populacionais diversos casos de TDAH iniciam na adolescência e na idade adulta. O Artigo #1 avaliou a existência de casos de início tardio e avaliou o período pré-mórbido desses indivíduos com TDAH de início na adolescência.

O segundo estudo tem o objetivo de testar novas abordagens para a classificação diagnóstica em psiquiatria, validando uma classificação objetiva baseada na testagem das funções executivas (FE) através de tarefas cognitivas. Abordagens objetivas que utilizam construtos da neurociência para estudo dos transtornos mentais são preconizadas pelo Research Domain Criteria (RDoC) – metodologia de pesquisa em

saúde mental que visa oferecer alternativas aos sistemas classificatórios vigentes ao aproximar a classificação dos conhecimentos de neurociência básica.

1.2. Sistemas Classificatórios em Psiquiatria: o DSM e a Fenomenologia Clássica

Os critérios diagnósticos em psiquiatria classicamente são baseados em modelos descritivos-fenomenológicos, tal qual dispostos nos principais manuais de classificação: o Manual Diagnóstico e Estatístico de Transtornos Mentais (DSM) e a Classificação Internacional de Doenças (CID). A operacionalização de tais critérios, iniciada a partir do lançamento do DSM-III em 1980 [1] foi de grande importância para superar dificuldades históricas da nosologia psiquiátrica: a baixa concordância diagnóstica entre avaliadores e falta de uma linguagem comum para classificação das condições que determinam sofrimento psíquico. Tal avanço da nosologia psiquiátrica foi em grande parte responsável pela melhoria do sistema diagnóstico, permitindo uma comunicação mais adequada entre profissionais e pacientes e também esteve associada aos progressos nas áreas de pesquisa clínica em saúde mental [2]–[4].

O embasamento teórico do modelo no qual o DSM está inserido baseia-se na ideia de interação epistêmica. Essa teoria pressupõe que o processo científico avança progressivamene rumo a uma verdade final por meio do enriquecimento teórico e auto-correção. Ou seja, o DSM seria um modelo que, apesar de falho, a cada atualização torna-se mais próximo de uma verdadeira apresentação natural dos transtornos mentais. De tal forma, a constante avaliação e testagem empírica dos critérios do DSM, além de ser essencial haja vista sua eventual arbitrariedade, é importante para o avanço da própria classificação diagnóstica baseada no modelo descritivo-fenomenológico.

Como um dos exemplo dessa testagem empírica, esforços tem sido realizados nas últimas décadas para verificação do critério etário necessário para o diagnóstico de TDAH.

1.3. Avaliação empírica de critérios diagnósticos: o caso do TDAH de início tardio

O TDAH é um dos mais prevalentes transtornos mentais da infância, acometendo cerca de 3.4% da população [5], associado com uma série de desfechos negativos, incluindo maiores comorbidades psiquiátricas, falhas acadêmicas e profissionais, acidentes, criminalidade, déficits econômicos e mortalidade precoce [6]. A condição é classificada como um transtorno do neurodesenvolvimento, caracterizado por sintomas de desatenção e/ou hiperatividade. Para seu diagnóstico, é necessário que o indivíduo apresente seis ou mais sintomas de desatenção e/ou hiperatividade (critério A) e que tais sintomas surjam antes de uma determinada idade (critério B) [7].

O critério B exige que os sintomas iniciem antes de uma idade pré-concebida, de forma que a apresentação sintomática ou que o prejuízo inicie na infância. As versões do DSM III (1980) [1] e IV (1994) [8] estabeleceram que a idade para o início de sintomas seria aos 7 anos. Este critério foi baseado na experiência clínica e na conceitualização do TDAH como um transtorno tipicamente da infância. No entanto, tal determinação foi estabelecida em um momento em que se careciam de evidências científicas capazes de determinar a validade dos pontos de corte do critério etário. A ausência da validação científica preocupava, pois, a inadequação de um critério diagnóstico poderia levar ao subdiagnóstico e subtratamento de casos reais.

O critério de idade de início dos sintomas foi contestado, inclusive propondo-se seu abandono até que surgissem evidências fortes que o sustentassem [9], [10]. No entanto, exista um temor por parte tanto da comunidade científica quanto da comunidade leiga que a flexibilização dos critérios diagnósticos do TDAH pudesse provocar grandes aumentos na prevalência do transtorno. Na atualização do DSM para a sua quinta versão, foi adotada uma postura intermediária: o aumento de 7 para 12 anos do critério etário. Tal definição foi feita de forma a manter o TDAH em sua perspectiva de transtorno de início precoce (e, portanto, primariamente pediátrico), porém considerando as evidências construídas que demonstravam que o aumento da faixa etária não provocaria aumento significativo da prevalência [11] e que não havia diferenças em resposta ao tratamento para casos que não cumpriam o critério etário anterior [12], [13].

No entanto, a pesquisa acerca desse ponto era baseada predominantemente em amostras clínicas e utilizava o relato dos pacientes ou familiares como fonte principal para determinação da idade de início dos sintomas. Estudos epidemiológicos robustos seriam necessários para investigar a real idade de início de sintomas e a ocorrência de casos de início tardio na população geral. O primeiro estudo a avaliar a ocorrência de casos de TDAH de início tardio em uma amostra populacional após as mudanças propostas pelo DSM-5 foi conduzido por Terrie Moffit (2015), utilizando a coorte de Dunedin. Esse estudo avaliou os participantes durante o final da infância e início da adolescência (11-15 anos) e novamente aos 38 anos, mostrando que 90% dos casos de TDAH na vida adulta não apresentavam esse diagnóstico na infância [14]. Tais achados, apesar de não poderem determinar precisamente a idade de início dos sintomas, demonstravam a prevalência de um grupo de pacientes com TDAH com incidência do

transtorno durante a adolescência e/ou idade adulta, ou seja, após o já estendido critério etário do DSM-5.

Esse estudo pioneiro levou a uma onda inicial de estudos epidemiológicos que objetivaram replicar os achados. As investigações conduzidas por Agnew-Blais na coorte Environmental Risk (E-Risk) Longtudinal Twin Study [15], Lucy Riglin na Avon Longitudinal Study of Parents and Children (ALSPAC) [16], e por Arthur Caye na Coorte de Pelotas [17] demonstraram a alta prevalência de casos de TDAH que incidiam após o critério etário. Esses estudos, no entanto, foram questionados acerca de suas limitações, principalmente no que se refere à inclusão de casos subsindrômicos de TDAH [18] e à melhor explicação do surgimento de sintomas de TDAH por condições comórbidas. O estudo de Margaret Sibley (2017) usando o Multimodal Treatment Study of ADHD (MTA) não evidenciou casos de TDAH de início tardio, considerando a melhor explicação dos sintomas de desatenção/hiperatividade por outras condições psiquiátricas e pelo uso de substâncias [19].

Uma nova onda de estudos populacionais foi realizada tendo em vista abordar tais limitações da literatura vigente. Uma reanálise dos dados da ASLPAC demonstrou que os participantes considerados como portadores de TDAH de início tardio já apresentavam maiores sintomas de TDAH na infância [20]. A avaliação acerca de TDAH de início tardio feito no estudo Child and Adolescent Twin Study in Sweden (CATSS) também apontou explicações alternativas para tais casos, incluindo a presença de mais diagnósticos psiquiátricos e traços de comportamento disfuncionais na infância desses participantes [21]. O outro estudo publicado nesse período faz parte dessa tese (Artigo #1), cujos resultados serão posteriormente discutidos.

1.4. Research Domain Criteria (RDoC) e métodos de classificação baseados nos dados

A existência de diversos critérios questionáveis no modelo descritivo-fenomenológico impulsionou a busca por métodos alternativos de classificação de pacientes. Essa busca também foi vista como uma oportunidade para estimular a pesquisa de base biológica, uma vez que os diagnósticos descritos pelo modelo fenomenológico apresentam uma série de entraves em sua validação com correlatos biológicos. As dificuldades relacionadas aos modelos vigentes estão baseadas em diversos conceitos, muitas vezes representando entraves significativos na prática clínica e na pesquisa, dos quais destacam-se: (a) a ausência de critérios objetivos como ferramentas diagnósticas além do relato clínico; (b) a instabilidade do curso dos transtornos mentais, frequentemente apresentando continuidades homo e heterotípicas ao longo da vida dos indivíduos acometidos; (c) as possibilidades de apresentação heterogêneas de fenótipos agrupados na mesma categórica diagnóstica; (d) a capacidade de múltiplas condições apresentarem fenótipos clínicos semelhantes, apresentando uma distinção com baixa validação, falhando em reconhecer possíveis mecanismos patofisiológicos comuns; (e) a dificuldade de estabelecer dicotomizações para apresentações muitas vezes dimensionais, criando empecilhos ao diagnóstico e determinando artificialmente a existência de casos subsindrômicos; e (f) as dificuldades em avançar no campo da pesquisa de marcadores biológicos utilizando o sistema classificatório vigente.

Dentro dessa perspectiva de mudança de paradigma, foi lançado em 2010 o Research Domain Criteria (RDoC) – uma iniciativa do National Institute of Mental Health (NIMH) que visa classificar os transtornos mentais tendo como base sua fisiopatologia

[22]. Ao propor a integração entre a neurociência moderna com a psicopatologia, o RDoC tem a intenção de criar um sistema classificatório que parte de mecanismos biológicos e finda na manifestação clínica (abordagem de baixo para cima). Essa perspectiva, embora usual em outras disciplinas médicas, contraria o processo histórico vigente da classificação e pesquisa em psiquiatria: a determinação do diagnóstico pelo modelo descritivo e a posterior busca de associações com correlatos neuropsicológicos e biomarcadores (abordagem de cima para baixo). Para tal, foi proposta uma matriz de sistemas que deveriam ser alvo das pesquisas utilizando a estratégia proposta pelo RDoC: valências positivas, valências negativas, sistemas cognitivos, processos sociais, excitação/modulação e sensoriomotor (Figura 1).

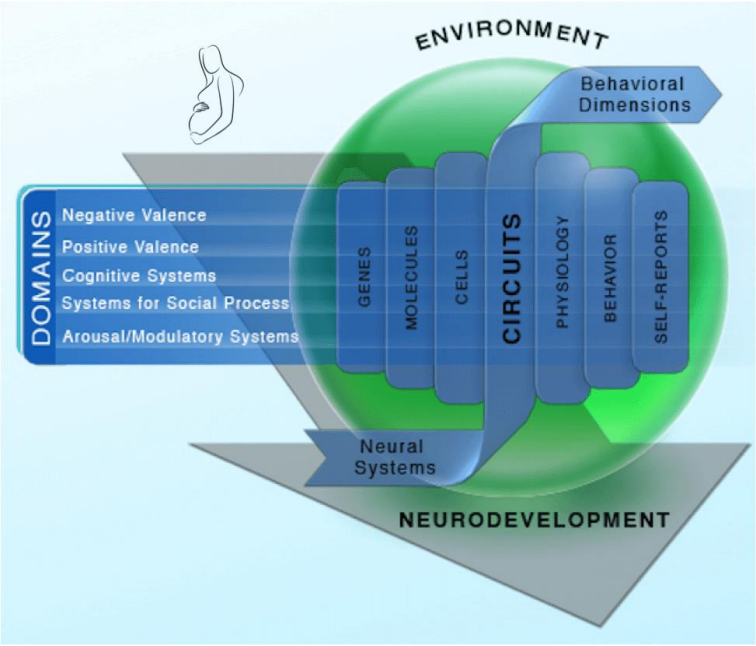


Figura 1 – Esquematização da estratégia do RDoC [23]

Esta iniciativa do RDoC ganhou força dentro de meios acadêmicos em decorrência da percepção da dificuldade em transpor para a clínica a grande quantidade

de achados de pesquisa realizados pelo campo da psiquiatria biológica e das neurociências nas últimas quatro décadas [24], [25]. Inicialmente, a tarefa proposta para o DSM-5 era de incorporar tais mecanismos biológicos na classificação vigente dos transtornos mentais [26]. No entanto, a equipe responsável pelo projeto do DSM-5 percebeu as complexidades, limitações e a provável precocidade de tentar incorporar a pesquisa em genética, neuroimagem e biomarcadores no processo de diagnóstico clínico [27]. Dessa forma, o DSM-5, lançado em 2013, manteve seu desenho descritivo-fenomenológico [7]. Pressupunha-se que o DSM deveria manter seu modelo por decorrência de sua validade clínica e o RDoC poderia tornar-se ferramenta científica para melhor explicação dos processos que levam aos transtornos mentais – sugerindo uma dicotomização temporária entre prática clínica e prática cientifica.

Passada uma década do lançamento do RDoC, a iniciativa e seus resultados preliminares seguem dividindo opiniões sobre sua utilidade tanto no campo dos pesquisadores, como entre os clínicos. A crítica ao RDoC aponta falhas no sistema, dentre as quais destacam-se: a arbitrariedade da sua matriz; o pressuposto não-confirmado de dimensionalidade em todos os processos mentais e psicopatológicos; e o abandono da perspectiva da história natural das doenças [28]. Por outro lado, os apoiadores do RDoC afirmam que este referencial permitiria a identificação de agrupamentos transdiagnósticos de pacientes com assinaturas biológicas semelhantes.

Esses grupos transdiagnósticos de pacientes normalmente são organizados utilizando métodos de clusterização[1] imputando variáveis biológicas com vistas a

[1] São considerados classicamente métodos de clusterização aqueles que utilizam técnicas mais ou menos modernas/robustas de Machine-Learning. Com essas técnicas, variáveis são imputadas no modelo que, sem a determinação a priori de um critério de classificação dos participantes, divide eles em clusters empíricos identificados pelo programa estatístico.

avaliação de apresentações clínicas. Nesse contexto, diversos estudos foram capazes de prover discernimentos acerca de processos biológicos associados ao aparecimento de fenótipos clínicos. Tal estratégia já foi utilizada para desenredar a reconhecida heterogeneidade das apresentações psiquiátricas[2] [29], tendo como foco de estudos a genética [30], a eletrofisiologia [31] a neuroimagem [32] e as funções cognitivas [33], reconhecidamente marcadores mais objetivos do que o relato sintomático.

1.5. Classificações Fenotípicas Objetivas

Novos sistemas classificatórios, como, por exemplo, o RDoC, deveriam pautar-se pela fisiopatologia e almejar maiores graus de objetividade em seus critérios. O desenvolvimento de métodos classificatórios com critérios que superem em parte a subjetividade do relato pessoal e que informem também acerca da patogenia do transtorno podem se tornar importantes ferramentas para categorização diagnóstica e determinação de informações preditivas sobre curso de doença, prognóstico e tratamento.

No entanto, os estudos que vem sendo realizados utilizando critérios biológicos como bases de classificação utilizam métodos de clusterização e, portanto, são altamente dependentes da amostra [29]. Ao proceder com um método de clusterização, apesar de haver ganho da força de consistência interna, perde-se a capacidade de validação e replicação em amostras externas, haja vista que a classificação é baseada

[2] O problema da heterogeneidade consiste em dois pontos principais: (1) a equifinalidade (as condições psiquiátricas são multideterminadas, de forma que um transtorno pode ser provocado por diversos mecanismos) e (2) a identificação de diversos subtipos em uma amostra a depender do foco de investigação. Em outras palavras, ao tentar identificar um padrão de características relacionados à um fenótipo, nosso resultado será dependente das especificadades das perguntas que estamos fazendo e dos mecanismos que estamos avaliando (neuropsicologia, genética, neuroimagem, etc).

em características próprias da amostra estudada. Além disso, a classificação por meio de validadores biológicos complexos, apesar de ser importante na perspectiva científica, não permite transpor os achados para a prática clínica cotidiana – que na imensa maioria das vezes não dispõe de recursos técnicos avançados (como neuroimagem e genotipagem). Dessa forma, os estudos atuais que tem em seu objetivo principal justamente a testagem de novas formas de classificação diagnóstica e propostas alternativas de nosologia afastam-se diametralmente da prática clínica.

A resolução dessas limitações da literatura vigente passa por duas tarefas: a seleção de variáveis objetivas que possam ser mais facilmente coletadas e a operacionalização de critérios de categorização das amostras que permitam a replicação dos estudos. O segundo artigo apresentado nessa tese tem como objetivo abordar essas duas limitações, utilizando como parâmetro objetivo a testagem das funções executivas (FE) (Artigo #2).

A escolha da avaliação da FE, principalmente baseadas na memória de trabalho e no controle inibitório, foi determinada por uma série de motivos: (a) Déficits de FE estão presentes em uma série de transtornos mentais, incluindo TDAH [34], [35], transtorno depressivo maior [36], transtorno bipolar [37] e esquizofrenia [38], [39]. Além disso, déficits em FE estão associados com a psicopatologia de forma geral [40], de forma que provavelmente tratam-se de marcadores transdiagnósticos; (b) Tais déficits estão associados à redução da qualidade de vida, menores realizações acadêmicas e dificuldades de relacionamento [41]–[43]. Adicionalmente, estão associados a uma maior incidência de comportamento impulsivo, que determinam piores desfechos em saúde física, abuso de drogas, status socioeconômico e encarceramentos na idade adulta [44]; (c) Avaliação da FE é facilmente realizada com

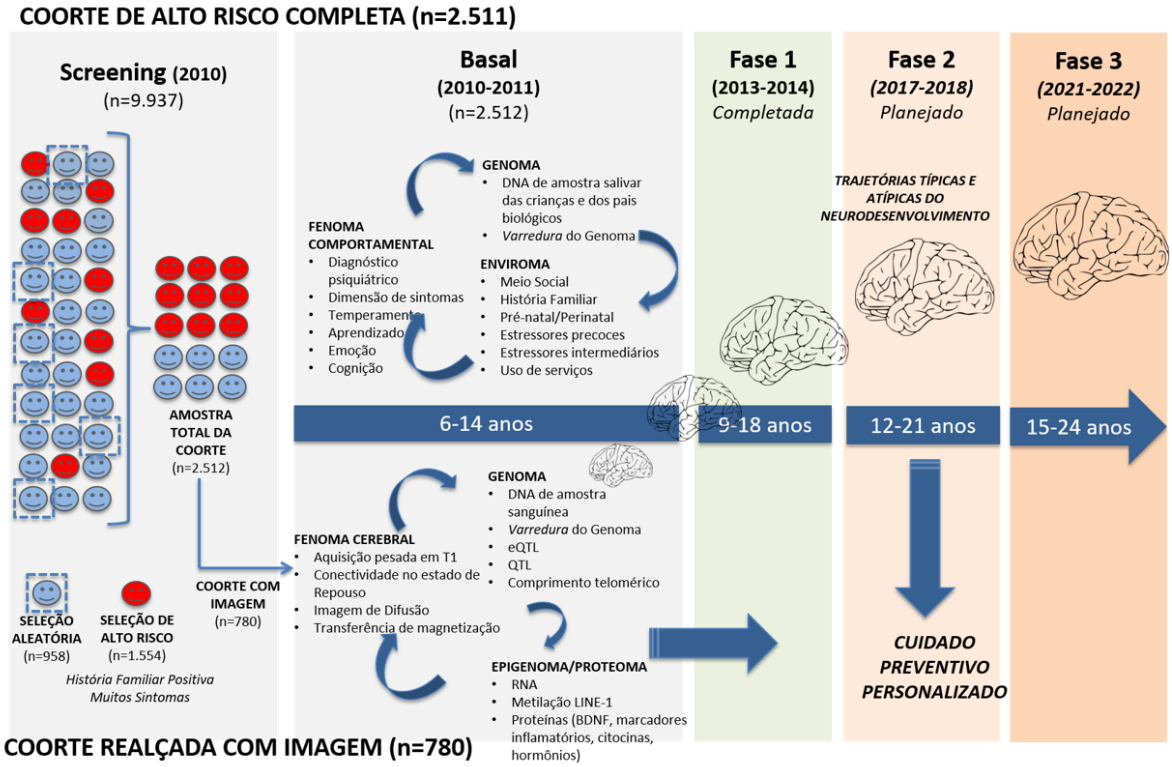
testes padronizados e com baixo custo que podem ser administrados por profissionais treinados sem a necessidade de aparelhagem complexa, além de apresentarem boa validação interna e externa [45]; e, por fim, (d) a FE, apesar de se assentarem um em componente biológico herdado, podem ser treinadas, de forma que intervenções podem ser oferecidas à grupos com déficits, desde que esses sejam corretamente identificados [46], [47].

Uma classificação baseada em um critério mais objetivos, tais quais tarefas de avaliação da FE, pode tornar-se uma ferramenta importante para identificação de indivíduos que não estão sendo avaliados completamente pelos critérios atuais. Essa classificação ganharia força caso possa ser operacionalizada de forma a ser testada e replicada, caso tenha capacidade preditiva para déficits importantes no funcionamento e caso associe-se a correlatos biológicos. A formulação de classificações fenotípicas objetivas, incluindo, mas não somente limitada às FE parecem estratégias relevantes para testar se estratégias "de cima para baixo", como o RDoC, e podem futuramente influenciar na prática clínica.

1.6. Nosologia Psiquiátrica na Infância e Adolescência: Investigação pelo Estudo Brasileiro de Alto Risco para Transtornos Psiquiátricos

O estudo do desenvolvimento típico e atípico na infância e adolescência é de grande importância para estabelecimento de critérios diagnósticos e para elaboração de teoriais patofiológicas para os transtornos mentais. Além disso, são importantes para o entendimento das trajetórias de neurodesenvolvimento, para identificação de fatores de risco para transtornos mentais e para planejamento de futuras intervenções. O projeto que embasa os estudos apresentados nessa tese objetiva avaliar justamente

esses aspectos. O Estudo Brasileiro de Alto Risco para Transtornos Psiquiátricos [48] é uma coorte comunitária de escolares organizada em Porto Alegre e São Paulo e desenvolvida pelo Instituto Nacional de Psiquiatria do Desenvolvimento. Trata-se de um estudo que inicialmente triou aproximadamente 10.000 famílias, constituindo uma coorte formada por 2.511 crianças e adolescentes (1.154 de alto-risco para transtornos mentais e 957 aleatoriamente selecionadas) que vem sendo seguidas desde 2009, sendo avaliadas e analisadas variáveis relacionadas à psicopatologia, cognição, genética e



neuroimagem (Figura 2).

Figura 2 – Desenho do Estudo Brasileiro de Alto Risco para Transtornos Psiquiátricos

A investigação completa e longitudinal desse grupo de jovens possibilita análise sobre as trajetórias do desenvolvimento típicos e de patologias e a adequação dos sistemas classificatórios em identificar e prever indivíduos que nelas se enquadram. Da

mesma forma, a base de dados coletada pela coorte permite a avaliação de critérios de classificação baseados nos próprios dados objetivos. Por fim, a justificativa para esta tese está baseada na constante modificação dos critérios classificatórios dos transtornos mentais e na necessidade de estudos referentes à identificação de falhas dos sistemas vigentes (Artigo #1) e avaliação de novas propostas para sistemas que podem ser utilizados no futuro (Artigo #2).

.

2. OBJETIVOS

3.1 Objetivo Geral

Estudar aspectos relacionados ao atual sistema de classificação diagnóstica em psiquiatria da infância e adolescência, avaliando limitações do sistema vigente para diagnóstico do TDAH (Artigo #1) e novas propostas de classificação guiadas pelos dados (Artigo #2).

3.2 Objetivos Específicos

a) Investigar a existência de casos de TDAH de início na adolescência (após os 12 anos de idade).

b) Avaliar o aspecto pré-mórbido dos casos de TDAH de início na adolescência, investigando psicopatologia dimensional, eventos escolares e testagens neuropsicológicas.

c) Avaliar os casos de TDAH de início na adolescência quanto aos seus escores poligênicos para TDAH, comparando à controles e casos normativos.

d) Testar a capacidade de operacionalização de uma classificação de disfunção executiva, baseada na testagem neuropsicológica objetiva.

e) Investigar a manifestação sintomática dos participantes classificados como pertencentes à classe de disfunção executiva.

f) Avaliar o impacto no funcionamento social, familiar e escolar dos participates pertencentes à classe de disfunção executiva.

g) Investigar validadores biológicos (genética e neuroimagem estrutural) dos participantes com disfunção executiva.

3. ARTIGO #1

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Heterotypic trajectories of dimensional psychopathology across the lifespan: the case of youth-onset Attention Deficit/Hyperactivity Disorder

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COMPETING INTERESTS

Arthur Manfro, Marcos Santoro, Pedro Pan, Fernanda Talarico, Sintia Belangero and **Giovanni Salum** declare no conflicts of interest. **Ary Gadelha** reports personal fees and non-financial support from Janssen, Ache Laboratórios Farmacêuticos and Daichii-Sankyo. **Rodrigo Bressan** reports grants and non-financial support from FAPESP, CNPq, and CAPES during the conduct of the study; he also reports grants, personal fees and non-financial support from Janssen, Ache Laboratórios Farmacêuticos, and Roche, outside the submitted work. **Elisa Brietzke** receives funding from CNPq, CAPES and FAPESP and also received speaker and advisory board payments from Daiichi-Sankyo. **Guilherme Polanczyk** is employed by the University of São Paulo. He receives grant or research support from CNPq, FAPESP, Fundação Maria Cecilia Souto Vidigal (FMCSV), Grand Challenges Canada, and the Bill and Melinda Gates Foundation. He has served as a consultant to Shire, Teva, and Medice; and has received royalties from Editora Manole. **Luis Augusto Rohde** has been a member of the speakers' bureau/advisory board and/or acted as a consultant for Eli-Lilly, Janssen-Cilag, Medice, Novartis and Shire in the last three years. He receives authorship royalties from Oxford Press and ArtMed. He has also received travel awards from Shire for his participation in the 2015 WFADHD meetings and from Novartis to take part of the 2016 AACAP meeting. The ADHD and Juvenile Bipolar Disorder Outpatient Programs chaired by him received unrestricted educational and research support from the following pharmaceutical companies in the last three years: Janssen-Cilag, Novartis, and Shire.

ABSTRACT

Background: recent studies have demonstrated the existence of a distinct late-onset ADHD trajectory. Our objective is to test the hypothesis if there are distinct ADHD trajectories regarding age of onset from childhood to adolescence and to compare clinical manifestations, cognitive functions and genetic risk for ADHD among distinct longitudinal groups.

Method: 924 children and adolescents from the community participated in the study. We compared clinical, cognitive features and genetic risk among four groups of participants: (1) childhood-limited, (2) youth-onset, (3) childhood-onset with youth persistence and (4) community comparisons without ADHD. Symptomatic and diagnostic assessments were performed using the Development and Well-Being Behavior Assessment, the Strengths and Difficulties Questionnaire and the Child Behavior Checklist. Cognitive functions were measured using a battery of standardized tests. Genetic risk for ADHD was calculating using summary statistics from the Psychiatric Genomics Consortium.

Results: half of the adolescents (52%) with ADHD had their symptom onset in adolescence. The impairment level of this group in adolescence is similar to the persistent group. Despite not having ADHD, the youth-onset group already presented in childhood more symptoms from other domains of psychopathology, higher shared variance in psychiatric symptomatology (p-factor), school impairment and executive dysfunctions than community comparisons. Furthermore, the youth-onset group presented lower levels of genetic risk for ADHD compared to other cases.

Conclusion: a significant proportion of adolescents with ADHD were youth-onset cases and presented similar impairment levels as those cases with early-onset ADHD. The

presence of cognitive impairments and higher levels of clinical symptoms in the youth-onset group already at childhood speaks in favor of a heterotypic trajectory of psychopathology suggesting that youth-onset ADHD might be an artificial consequence of categorizing dimensional psychopathology into discrete diagnostic groups.

Key-Words: youth-onset; executive function; cognition; polygenic risk scores; p-factor.

INTRODUCTION

Attention Deficit/Hyperactivity Disorder (ADHD) is traditionally conceptualized as a neurodevelopmental disorder with onset before the age of 12 that can persist into adolescence and adulthood (American Psychiatry Association, 2013). Therefore, current classifications state that ADHD cases observed in adolescence or adulthood represent the symptomatic persistence from childhood through the individual's lifespan. In the last years, however, new evidence has emerged questioning this traditional view of the disorder, and the late-onset ADHD started to be a focus of empirical interest.

In 2015, Moffit and collaborators published a pioneering study demonstrating that nearly 90% of adult ADHD cases in the Dunedin cohort were *de novo* cases (Moffitt et al., 2015). Investigators replicated the findings on the existence of late-onset ADHD in three other large cohort samples: E-Risk (Agnew-Blais et al., 2016), Pelotas Birth Cohort (Caye et al., 2016) and ALSPAC (Cooper et al., 2018; Riglin et al., 2016). These findings raised a debate on whether adult ADHD could be considered a childhood-onset neurodevelopmental disorder, questioning whether late-onset ADHD might represent a distinct disorder from childhood-onset ADHD (Castellanos, 2015; Moffitt et al., 2015). Other reports, however, are somewhat more conservative, raising concerns about

unidentified subthreshold ADHD (Faraone & Biederman, 2016) or better diagnostic explanation by other psychiatric comorbidities (Sibley et al., 2017).

The current literature presents some limitations. *First*, most community studies did not investigate if the ADHD onset was in adulthood or adolescence. Analysis of the participants of the Dunedin, E-Risk, and Pelotas studies considered a first assessment in childhood and posterior assessments already in adulthood. Thus, the emergence of ADHD symptoms might have occurred any time during adolescence or adulthood in those studies. The first ALSPAC study (Riglin et al., 2016), which assesses adolescents, did not primarily aim to investigate a specific adolescent-onset trajectory of ADHD. However, more recently, the ALSPAC data were re-analyzed in order to specifically investigate an ADHD onset in adolescence (Cooper et al., 2018). This study showed that there is a distinct group of adolescent-onset cases, despite the fact that a large proportion of these potential youth-onset cases were actually misclassified on the basis of their earlier SDQ hyperactivity scores. The MTA study (Sibley et al., 2017), on the other hand, found the majority of the ADHD onset in adolescence for late-onset cases, but the local normative control group from where late-onset cases were investigated was not a population sample. Therefore, the question of whether late-onset ADHD can, in fact, be a phenomenon occurring predominantly during adolescence (and not adulthood) still needs further investigation. *Second,* the recent study for the ALSPAC cohort (Cooper et al., 2018) indicates the importance of specific strategies to exclude subthreshold ADHD cases in childhood, something that has not been addressed in other population-based studies. Since DSM-5 ADHD criteria state that *several* of the ADHD symptoms have to start before the age of 12, to assure the validity of a late-onset ADHD conception, the inclusion in this group should be based on asymptomatic children

or children with very few symptoms in childhood, an analysis still to be performed in population studies. *Third,* few studies so far have investigated between-group differences in features of ADHD cognition, such as executive function and basic processing efficiency (Moffitt et al., 2015). Studying these cognitive issues is relevant since deficits might precede symptomatic onset and provide clues on which deficits might be predictive of incident ADHD later in life. *Fourth*, no study has investigated between-group differences in dimensional assessments and particularly the theorized general susceptibility to psychiatric disorders– the so-called p-factor et al., 2017; Martel et al., 2017), which, despite controversies on its significance and relevance (van Bork et al., 2017), indexes a high level of overall symptomatology shared among several psychiatric disorders (Caspi et al., 2014). *Lastly*, no study has investigated between-group differences in ADHD onset and trajectory using the new GWAS findings and genetic risk scores from the Psychiatric Genomics Consortium (PGC) (Sullivan et al., 2017).

The aim of the current study is to compare clinical manifestations, cognitive functions and genetic risk for ADHD for individuals with distinct onsets and trajectories of ADHD symptoms from childhood to adolescence. Participants are members of the Brazilian High-Risk Cohort (Salum et al. 2015), who were prospectively assessed at ages 6-12 in the baseline assessment and at ages 12-17 in the 3-year follow-up assessment. Three ADHD trajectories (Childhood-Limited, Youth-Onset, and Persistent Cases) and a Community-Ascertained Comparison were compared hypothesizing that youth-onset cases already presented higher general psychopathology traits before ADHD diagnosis.

METHODS

Sample description

Our study is composed of participants from two waves of the Brazilian High-Risk Cohort, a school-based community cohort from two Brazilian cities: Porto Alegre and São Paulo. The 2511 children who participate in the study (1554 high-risk for psychiatric disorders and 957 randomly selected) were thoroughly assessed with detailed psychiatric instruments and neurocognitive tests. Detailed information about the cohort is found in other publication (Salum et al. 2015). Follow-up interviews were conducted on average three years later when 2010 children and adolescents were re-evaluated. This study was approved by the ethical committee of the University of São Paulo. Informed consent was obtained from the parents of all participants.

ADHD diagnosis

Parents were interviewed with the Development and Well-Being Assessment (DAWBA), a structured questionnaire based on DSM-IV diagnostic criteria which is well suited for epidemiological studies (Goodman, Ford, Richards, Gatward, & Meltzer, 2000). An algorithm following DSM criteria defined ADHD diagnosis: 6 or more symptoms of inattention and/or 6 or more symptoms of hyperactivity, considering that those symptoms should be present with some degree of impairment in 2 or more contexts (e.g., school and home). For the purposes of this study, the age of symptoms onset was not considered as a criterion for ADHD diagnosis.

Sample selection

Considering that retrospective parent-reports may not correctly inform the age of onset of ADHD, we performed an age-based selection procedure to select our

subsample for this study. We exclude all participants over 12 years old at the baseline assessment and all participants below 12 years old at the follow-up assessment. These exclusion criteria were performed to improve sample reliability and dismiss the use of parent reports for the age of onset. Based on two assessments, we classified participants into four longitudinal groups:

(1) Community comparisons, CC – children with no more than 2 ADHD symptoms at either baseline or follow-up and with no other mental disorder at baseline (n=806);

(2) Childhood-limited ADHD, CL – children with ADHD diagnosis at baseline assessment and with no more than 2 ADHD symptoms at follow-up (n=64);

(3) Youth-onset ADHD, YO – children with no more than 2 ADHD symptoms at baseline and ADHD diagnosis at follow-up (n=28);

(4) Persistent ADHD, Per – children with ADHD diagnosis both at baseline and follow-up assessments (n=26).

The inclusion of subjects only in the age range assessed (6-12 years at baseline and 12-17 years at follow-up) reduced the sample size from 2010 to 1317. Moreover, the conservative criterion used to exclude subthreshold ADHD cases further reduced the sample size from 1317 to 924 individuals, as depicted above. Exclusion of subthreshold ADHD cases was based on the predefined arbitrary limit of 2 ADHD symptoms.

Dimensional assessments and other psychiatric features

Dimensional scales

Participants were compared using the Strengths and Difficulties Questionnaire (SDQ), which is a short, well-validated instrument to assess dimensional domains of

psychopathology. Both SDQ parent and teacher-reports were evaluated at the baseline. At the follow-up assessment, only SDQ parent-reports were available. Also, participants were compared at baseline and follow-up using the parent reports of the Child Behavior Checklist (CBCL), a largely used and well-validated instrument (Achenbach & Ruffle, 2000; Ivanova et al., 2007). ADHD-related and hyperactivity domains were excluded from main analysis since group selection procedures were already based on the number of ADHD symptoms.

P-factor assessment

To calculate individuals' p-factor, i.e., the shared variance in psychiatric symptomatology, we used the DAWBA bands as reported in previous studies (Martel et al., 2017). DAWBA bands are computer-generated categories based on answers to the DAWBA questions that inform about the probability of a specific psychiatric diagnosis. This model encompasses one common factor (p-factor) and three dissociable dimensions: fear, distress and externalizing domains. As previously reported by our research group, this model best described the structure of psychopathology as measured by DAWBA bands and provided an excellent fit to the data and high reliability for the p-factor our specific cohort (Martel et al., 2017).

Cognitive function assessment

Executive function

Executive function assessment took place in the participants' school over four sections conducted by trained mental health professionals. Executive function was measured by using a second-order model including a higher executive function factor

encompassing three lower order factors measured by well-validated tasks: working memory [Digit span (Vandierendonck, Kemps, Fastame, & Szmalec, 2004), and Corsi blocks task (Vandierendonck et al., 2004)], inhibitory control [Conflict control task (Hogan, Vargha-Khadem, Kirkham, & Baldeweg, 2005) and Go/no-go (Bitsakou, Psychogiou, Thompson, & Sonuga-Barke, 2008)], and temporal processing [Time anticipation (Toplak & Tannock, 2005)]. The description of the tasks and the model fit are described elsewhere (Martel et al., 2017) and also are briefly described in the supplemental material, available online. All measures were adjusted for age and transformed into z *scores* before data analysis.

Basic information processing

Basic information processing variables were derived from diffusion models (Ratcliff & McKoon, 1988; White, Ratcliff, Vasey, & McKoon, 2010) based on a simple two-choice reaction time task (2C-RT, description available in the supplemental material). Diffusion models were used to decompose 2C-RT into the distinct components of basic information processing: processing efficiency (determined by the drift rate), speed-accuracy trade-off (measured as boundary separation) and encoding/motor function (measured as non-decision time). Previous investigations (Salum, Sergeant, et al., 2014; Salum, Sonuga-Barke, et al., 2014) showed important basic processing differences in children with distinct levels of ADHD symptomatology. More information on this methodology can be found in other publications (Salum, Sergeant, et al., 2014; Salum, Sonuga-Barke, et al., 2014).

Polygenic Risk Score

DNA was extracted from blood or saliva from the participants and genotyping was performed using the HumanOmniExpressV1 (Illumina). Polygenic risk scores were calculated with the PRSice software (Euesden, Lewis, & O'Reilly, 2015) and derived from summary statistics of the newest GWAS (June 2017) from the Psychiatric Genomics Consortium and iPSYCH (available at https://www.med.unc.edu/pgc/results-and-downloads). P-value-informed clumping was performed retaining the SNP with the smallest P-value within a 250-kb window and excluding those SNPs in linkage disequilibrium ($r2 > 0.1$). Multiple thresholds were evaluated, ranging from 0.001 (1,849 single nucleotide polymorphisms) to 0.8 (207,512 single nucleotide polymorphisms). The best threshold was defined based on the better-explained variance between CC and all ADHD cases. Previous studies have shown that polygenic risk scores for ADHD are higher in patients with the disorder (Hamshere et al., 2013) and are also associated with ADHD symptom levels in the population (Martin, Hamshere, Stergiakouli, O'Donovan, & Thapar, 2014). Polygenic risk scores were transformed into *z scores,* and analysis was adjusted for the four principal components which account for ancestry. Polygenic risk scores were available only for a subsample of 290 subjects distributed into the following groups: CC (n=245), CL (n=25), YO (n=8) and Per (n=12).

Statistical analysis

Groups were compared by using Chi-Square tests, ANOVAs, and ANCOVAs. Post-hoc tests were performed comparing each group to the youth-onset group, given our study hypothesis. ADHD incidence and persistence in the 3-year follow-up were analyzed using logistic regressions. Data analysis was performed using SPSS version 23 and R software version 3.4.2.

RESULTS

Sample description

Most childhood ADHD cases remitted and did not fulfill diagnostic criteria in adolescence (71%). From the 54 ADHD cases in adolescence, 28 (52%) had its onset in adolescence, showing that, at follow-up, half of the subjects with ADHD were *de novo* cases (YO). There were no between-group differences in sex, ethnicity, age and socioeconomic status. Sample information is depicted in Table 1.

ADHD presentation and dimensional assessments.

The YO group had a significantly higher overall total number of psychiatric symptoms (excluding ADHD symptoms) in both SDQ parent and teacher reports when compared to CC at baseline. Results were replicated using the parent-rated CBCL, showing YO group to significantly differ from CC in total, internalizing and externalizing scores. Violin plots and density plots concerning baseline SDQ and CBCL scores are shown in Figure 1. Complete information on dimensional assessments can be found in the Table S1 from supplemental material, available online. We further divided groups into quartiles regarding CBCL scores and main domains on baseline assessment, indicating that the minority of the YO group (10.7%) were among children with few symptoms before age 12 and a large proportion (53.6%) already presented high levels of symptoms. Complete quartile analysis can be found in table S2 of the supplemental material, available online.

Shared variance in psychiatric symptomatology: p-factor

Groups were also compared concerning their p-factor and specific domains of psychopathology (fear, distress and externalizing) in the baseline. YO displayed significantly higher scores in p-factor and externalizing when compared to CC, showing increased scores on the shared variance among all psychiatric disorders (MD=0.196, p=0.002) and also in the specific externalizing domain (MD=0.167, p=0.012). No differences were observed in fear and distress domains. Complete data on this analysis can also be found in Table S2, available online.

Psychiatric comorbidities, medication and substance use

Baseline assessment showed that most of the YO group did not have other categorical psychiatric diagnoses before age 12 (only 3 participants with oppositional defiant disorder and 1 with depression). Also, no member of the YO group was on psychiatric medications at this assessment. In the follow-up assessment, YO group presented significantly higher rates of oppositional defiant/conduct disorder than CC. Groups did not statistically differ in alcohol, tobacco or illicit drugs use at follow-up. The clinical description of the sample can be seen in Table 2.

To evaluate if YO cases could be consequences of other formal comorbidities in the follow-up assessment in adolescents, we performed an exclusion analysis to determine the number of non-comorbid YO ADHD cases (excluding adolescents with any depression, anxiety and conduct disorders at follow-up). From the 28 YO cases, 12 (43%) were non-comorbid, showing that other comorbidities could not explain a large proportion of YO ADHD cases from our sample.

Intelligence, cognitive assessment and school performance.

Analysis of intelligence, executive function, basic processing efficiency and school performance used data gathered at baseline. Comparisons demonstrated that YO had a worse global executive function scores (MD=-1.163, p=0.026), due to deficits in temporal processing (MD=-2.304, p=0.017). The YO group also showed worse academic performance (MD=-0.435, p=0.009), reading scores (MD=-7.313, p=0.009), writing scores (MD=-6.294, p<0.001), and a higher frequency of adverse school events when compared to CC. However, YO did not differ from CC in other features of ADHD cognition, such as basic information processing (mean drift rate, mean non-decision time and boundary separation, all p>0.05). Data regarding cognitive evaluation is depicted in Table 3.

Predictors of persistence and incidence.

Logistic regressions were performed to evaluate predictors of both persistence (CL and Per groups) and incidence (TDC and YO groups) of ADHD in adolescence. Persistence was predicted by the total of symptoms at baseline (OR=1.368, p=0.001). Regarding incidence, the analysis showed that higher socioeconomic scores (OR=1.111, p=0.016) and lower executive function (OR=0.824, p=0.030) significantly predicted new cases. Complete data on logistic regression models can be found in Table S3 from supplemental material, available online.

Polygenic Risk Score

Among the multiple thresholds, results were similar with a better-explained variability for 0.143 threshold (comparing CC to all ADHD cases). Using the most similar available threshold (0.1), YO presented a lower polygenic risk score when compared to

CC (MD=0.742, p=0.047), CL (MD=1.126, p=0.007), and Per (MD=1.161, p=0.012). Other thresholds also showed that polygenic risk scores were elevated for childhood-onset cases (CL and Per) but not to adolescent-onset cases (YO). Differences in polygenic risk scores for the multiple thresholds are shown in Figure 2.

DISCUSSION

Our study brings new findings for the ongoing debate on late-onset ADHD by providing data on ADHD youth-onset in a community sample of adolescents, a group still understudied in the field. We found that 52% of ADHD cases occurring after childhood were *de novo* cases, a finding consistent with the late-onset literature in community studies but now demonstrated in adolescents. The ADHD cases in our study presented all DSM symptomatic, pervasiveness and impairment criteria for ADHD diagnosis, demonstrating the clinical prominence of this group. A follow-back analysis found YO group to display several signs of symptomatology before the diagnostic onset, consisting of more symptoms from other domains of psychopathology, higher p-factor, and also higher school impairment and temporal processing dysfunctions when compared to community comparisons. Groups of ADHD cases in adolescence (youth-onset and persistent) differed on the age of onset, but showed important similarities concerning comorbidity profile and also an overall similar level of impairment, also demonstrating clinical importance of the youth-onset group. Our genetic analysis revealed lower genetic risk for childhood ADHD based on polygenic risk scores if compared to community ascertained comparison and ADHD cases.

Despite doubts and concerns regarding the late-onset of ADHD, it has become clear that trajectories of the condition starting after the age of onset criterion of DSM

may be significant in adolescence. The ongoing debate on late-onset ADHD is based mainly on two reasonable hypotheses: the existence of unidentified subthreshold ADHD cases (Faraone & Biederman, 2016) and the better explanation of ADHD symptoms in older subjects as a consequence of other conditions (Sibley et al., 2017). Results from our research show that the late-onset ADHD is prevalent and that between-group differences against community comparisons exist despite the exclusion of the subthreshold ADHD cases. Furthermore, regarding the second hypothesis, we showed that a significant proportion of YO ADHD cases could not be explained by other psychiatric comorbidities, demonstrating the importance to look for other explanations.

With the presented study, we propose a different hypothesis on youth-onset ADHD phenomenology which relies on observing robust evidence that psychopathology in childhood is formed by multiple transitional dimensions (Copeland et al., 2013; Shevlin, McElroy, & Murphy, 2017), and therefore not a simple discrete phenomenon with a single manifestation over time (e.g., ADHD). Assuming that, we hypothesize that the late-onset ADHD phenotype might be a consequence of combining (a) high levels of overall susceptibility to psychiatric disorders, but failing to meet a clinical threshold for a psychiatric disorder in early life with (b) the well-known heterotypic transitions in symptom manifestations over development (i.e., children with emotional and behavior symptoms in childhood presenting with inattention and hyperactivity meeting clinical threshold later in life). Dichotomizing multiple expressions of dimensional psychopathology might cause confusion when assessing trajectories of psychopathology, especially when the clinical condition includes age on onset in its diagnostic criteria, as it occurs with ADHD. Our study suggests that arbitrarily categorizing the onset and the severity of a dimensional and dynamic psychopathology

can produce syndromes for which the boundaries between normal and abnormal (and between distinct syndromes) are blurred. Therefore, the late-onset ADHD phenomena might represent another example of problems assigning caseness status for dimensional manifestations of psychopathology over the lifespan. This is consistent with previous evidence showing the prominence of a general factor of psychopathology – the p-factor - which may manifest in distinct ways over development and wax and wane over time (Caspi et al., 2014; Caspi & Moffitt, 2018; Lahey et al., 2017; Martel et al., 2017).

Psychiatric disorders can present in different ways in the subject's development (Copeland et al., 2013; Pine & Fox, 2015; Shevlin et al., 2017). Main trajectories of psychiatric disorders, such as ADHD, are based on the following: homotypical persistence (as observed in the persistent group), sustained remissions (as observed in the childhood-limited group), heterotypical transitions and late-onset cases (both which can be seen in the youth-onset group). We showed here that increased levels of dimensional psychopathology were found in youth-onset cases and, therefore, that heterotypical transitions at the subthreshold (or dimensional levels) may explain most of these cases. Nevertheless, one cannot exclude completely the existence of pure late-onset cases, i.e., adolescent ADHD cases with very low symptoms from all other domains of psychopathology at baseline; however, they are likely to be less common than YO cases with already increased levels of symptoms from other domains. In any case, those longitudinal group trajectories are representative of the multiple possibilities of phenotypic expression of a dimensional psychopathology which partially shares common causes (Brain Consortium et al., 2018). This shared causes and theorized general susceptibility are also hypothesized by the p-factor theory (Caspi et al., 2014; Caspi & Moffitt, 2018; Lahey et al., 2017; Martel et al., 2017). Despite that, it is important

to mention that there are alternative interpretations of the p-factor phenomenon (Caspi & Moffitt, 2018), and criticisms of the interpretation of the model (van Bork et al., 2017).

Corroborating our post-hoc hypothesis, adolescents with youth-onset ADHD have not only more symptoms in both parent and teacher reports, but also lower cognitive and school performance than community comparisons as children, before they reach the diagnostic threshold. It was known that these dysfunctions are important components of the neuropsychology of ADHD (Salum, Sergeant, et al., 2014; Salum, Sonuga-Barke, et al., 2014; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). These findings on early cognitive markers were not found in previous cohort studies but might be relevant for adolescent-onset ADHD. It is also notable that deficits in basic information processing, which have been shown to be important features of ADHD pathophysiology (Salum, Sergeant, et al., 2014; Salum, Sonuga-Barke, et al., 2014), did not differ between the youth-onset group and community comparisons. The existence of school performance deficits and a high number of adverse school events corroborates the idea that these children already present levels of impairment.

Our findings on the new ADHD polygenic risk scores are consistent with previous late-onset ADHD literature (Moffitt et al., 2015; Riglin et al., 2016), by not showing an increased genetic risk for ADHD in YO group. Nevertheless, previous evidence from behavioral genetic studies corroborates our findings. Longitudinal ADHD data from other studies have shown that interindividual changes in ADHD symptoms were explained by genetic influences that were largely distinct from the ones that influenced the baseline level of symptoms (Pingault et al., 2015). In this perspective, it is fair assumption that the number of ADHD symptoms in childhood and ADHD trajectories (including late-onset trajectories) may be influenced by distinct genetic and

environmental factors. However, our results concerning polygenic risk scores must be seen with caution, because of the small sample size with available genetic data.

Alternative hypotheses on the origins of the youth-onset phenomenon found in our study should also be discussed. It is still possible that youth-onset cases were better explained by subthreshold symptoms from comorbid conditions that could be mimicking inattention and hyperactivity in some cases. Also, it is possible that youth-onset cases were delayed presentations of normative childhood-onset ADHD that did not emerge in childhood due to resilience factors (such as higher socioeconomic status), lower dosage of risk factors (such as lower polygenic risk scores) or with symptoms that lead to lower impairment (such as less academic performance problems in childhood when compared to childhood ADHD cases). It is also possible that some ADHD cases had a more wax and wane course, in which symptoms could disappear in late-childhood and reappear in adolescence depending on environmental demands. Since our study presents a single assessment of psychopathology in childhood, some of these trajectories might not be identifiable. However, by the adoption of a strict criterion to define the absence of ADHD diagnosis, it is unlikely that youth-onset cases were actually misclassified. In fact, it may be hypothesized that these lower loads of risk factors, aligned with a non-specific symptomatic presentation in childhood could be markers of a form of ADHD which presents later in life.

Limitations of our study should be noted. *First*, the subject's parents answered most of the instruments used in data collection. Even though parents are a reliable source to investigate psychological constructs in children, self-reports could provide valuable information for adolescents. However, considering that parent-reports are more reliable in childhood, the use of self-reports in adolescence could artificially inflate

differences between assessments, based solely on the differences between informant sources. Also, there is consistent evidence in the literature showing that individuals with ADHD may not be the best reporters of their symptoms even when older (Knouse, Bagwell, Barkley, & Murphy, 2005; Molina & Sibley, 2014; Sibley et al., 2012). Furthermore, SDQ teacher-reports also supported the differences between YO and CC seen in parent-reports, improving the reliability of our analysis. *Second,* even though our sample was comprised of 924 individuals, only 118 are defined as ADHD cases according to trajectories criteria, and the youth-onset group is composed of 28 individuals. On the other hand, this numeric imbalance is inherent in cohort designs and has also been a rule in other studies regarding late-onset ADHD. Also, by adopting stricter criteria to define longitudinal groups, we have decreased the number of individuals but strengthened our findings. *Lastly*, considering that there was an average three years gap between baseline and follow-up assessments, timing of incidence and remission of ADHD cases cannot be precisely determined. This is important since some of the youth-onset cases may have started symptoms before the age of 12, therefore fulfilling DSM-5 age of onset criteria. On the other hand, this limitation does not contradict core findings of our research regarding dimensionality and cognitive impairments, even more considering that the very concept of youth is being expanded to cover from 10-24 years old (Patton et al., 2018), a time interval in which our YO cases do apply. Nonetheless, we performed a sensitivity analysis for a subsample of 11-12 years old at baseline, assuring that ADHD incidence would occur after 12 years old. Results from this analysis confirmed most of our findings and are further discussed in the supplemental material, available online.

Our findings demonstrate that there is a distinct ADHD trajectory, concerning the age of onset, that begins in adolescence and that this trajectory is preceded by early markers of temporal processing dysfunction, symptoms in other psychiatric domains, school impairment, and higher general psychopathology traits in childhood. The overall presentation of this condition speaks in favor of the hypothesis that our sometimes artificial categorization of psychiatric symptoms might make even more complex understanding the dimensional and heterotypic psychopathological trajectories. So far, however, it seems fair to conclude that there are ADHD cases with an adolescent-onset which should be taken into consideration by clinicians and researchers working in the field.

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REFERENCES

Achenbach, T. M., and T. M. Ruffle. "The Child Behavior Checklist and Related Forms for Assessing Behavioral/Emotional Problems and Competencies." *Pediatrics in Review* 21, no. 8 (August 1, 2000): 265–71. https://doi.org/10.1542/pir.21-8-265.

Agnew-Blais, Jessica C., Guilherme V. Polanczyk, Andrea Danese, Jasmin Wertz, Terrie E. Moffitt, and Louise Arseneault. "Evaluation of the Persistence, Remission, and Emergence of Attention-Deficit/Hyperactivity Disorder in Young Adulthood." *JAMA Psychiatry* 73, no. 7 (July 1, 2016): 713. https://doi.org/10.1001/jamapsychiatry.2016.0465.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders.5th ed. Washington, DC: American Psychiatric Association; 2013.

Bitsakou, P., L. Psychogiou, M. Thompson, and E. J. S. Sonuga-Barke. "Inhibitory Deficits in Attention-Deficit/Hyperactivity Disorder Are Independent of Basic Processing Efficiency and IQ." *Journal of Neural Transmission* 115, no. 2 (February 2008): 261–68. https://doi.org/10.1007/s00702-007-0828-z.

Brainstorm Consortium, Verneri Anttila, Brendan Bulik-Sullivan, Hilary K. Finucane, Raymond K. Walters, Jose Bras, Laramie Duncan, et al. "Analysis of Shared Heritability in Common Disorders of the Brain." *Science (New York, N.Y.)* 360, no. 6395 (22 2018). https://doi.org/10.1126/science.aap8757.

Bork, Riet van, Sacha Epskamp, Mijke Rhemtulla, Denny Borsboom, and Han L. J. van der Maas. "What Is the P-Factor of Psychopathology? Some Risks of General Factor Modeling." *Theory & Psychology* 27, no. 6 (December 1, 2017): 759–73. https://doi.org/10.1177/0959354317737185.

C. Patton, George, Craig A. Olsson, Vegard Skirbekk, Richard Saffery, Mary Wlodek, Peter S. Azzopardi, Marcin Stonawski, et al. "Adolescence and the next Generation." *Nature* 554 (February 21, 2018): 458–66. https://doi.org/10.1038/nature25759.

Caspi, Avshalom, Renate M. Houts, Daniel W. Belsky, Sidra J. Goldman-Mellor, HonaLee Harrington, Salomon Israel, Madeline H. Meier, et al. "The p Factor: One General Psychopathology Factor in the Structure of Psychiatric Disorders?" *Clinical Psychological Science* 2, no. 2 (March 2014): 119–37. https://doi.org/10.1177/2167702613497473.

Caspi, Avshalom, and Terrie E. Moffitt. “All for One and One for All: Mental Disorders in One Dimension.” *The American Journal of Psychiatry*, April 6, 2018, appiajp201817121383. https://doi.org/10.1176/appi.ajp.2018.17121383.

Castellanos, F. Xavier. “Is Adult-Onset ADHD a Distinct Entity?” *American Journal of Psychiatry* 172, no. 10 (October 2015): 929–31. https://doi.org/10.1176/appi.ajp.2015.15070988.

Caye, Arthur, Thiago Botter-Maio Rocha, Luciana Anselmi, Joseph Murray, Ana M. B. Menezes, Fernando C. Barros, Helen Gonçalves, et al. “Attention-Deficit/Hyperactivity Disorder Trajectories From Childhood to Young Adulthood: Evidence From a Birth Cohort Supporting a Late-Onset Syndrome.” *JAMA Psychiatry* 73, no. 7 (July 1, 2016): 705. https://doi.org/10.1001/jamapsychiatry.2016.0383.

Cooper, Miriam, Gemma Hammerton, Stephan Collishaw, Kate Langley, Ajay Thapar, Søren Dalsgaard, Evie Stergiakouli, et al. “Investigating Late-Onset ADHD: A Population Cohort Investigation.” *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, April 23, 2018. https://doi.org/10.1111/jcpp.12911.

Copeland, William E., Carol E. Adair, Paul Smetanin, David Stiff, Carla Briante, Ian Colman, David Fergusson, et al. “Diagnostic Transitions from Childhood to Adolescence to Early Adulthood.” *Journal of Child Psychology and Psychiatry, and Allied Disciplines* 54, no. 7 (July 2013): 791–99. https://doi.org/10.1111/jcpp.12062.

Euesden, Jack, Cathryn M. Lewis, and Paul F. O’Reilly. “PRSice: Polygenic Risk Score Software.” *Bioinformatics (Oxford, England)* 31, no. 9 (May 1, 2015): 1466–68. https://doi.org/10.1093/bioinformatics/btu848.

Faraone, Stephen V., and Joseph Biederman. “Can Attention-Deficit/Hyperactivity Disorder Onset Occur in Adulthood?” *JAMA Psychiatry* 73, no. 7 (July 1, 2016): 655. https://doi.org/10.1001/jamapsychiatry.2016.0400.

Goodman, R., T. Ford, H. Richards, R. Gatward, and H. Meltzer. “The Development and Well-Being Assessment: Description and Initial Validation of an Integrated Assessment of Child and Adolescent Psychopathology.” *Journal of Child Psychology and Psychiatry, and Allied Disciplines* 41, no. 5 (July 2000): 645–55.

Goodman, R., T. Ford, H. Simmons, R. Gatward, and H. Meltzer. “Using the Strengths and Difficulties Questionnaire (SDQ) to Screen for Child Psychiatric Disorders in a Community Sample.” *The British Journal of Psychiatry: The Journal of Mental Science* 177 (December 2000): 534–39.

Hamshere, Marian L., Kate Langley, Joanna Martin, Sharifah Shameem Agha, Evangelia Stergiakouli, Richard J. L. Anney, Jan Buitelaar, et al. “High Loading of Polygenic Risk for ADHD in Children with Comorbid Aggression.” *The American Journal of Psychiatry* 170, no. 8 (August 2013): 909–16. https://doi.org/10.1176/appi.ajp.2013.12081129.

Hogan, Alexandra M., Faraneh Vargha-Khadem, Fenella J. Kirkham, and Torsten Baldeweg. “Maturation of Action Monitoring from Adolescence to Adulthood: An ERP Study.” *Developmental Science* 8, no. 6 (November 2005): 525–34. https://doi.org/10.1111/j.1467-7687.2005.00444.x.

Ivanova, Masha Y., Thomas M. Achenbach, Levent Dumenci, Leslie A. Rescorla, Fredrik Almqvist, Sheila Weintraub, Niels Bilenberg, et al. “Testing the 8-Syndrome Structure of the Child Behavior Checklist in 30 Societies.” *Journal of Clinical Child & Adolescent Psychology* 36, no. 3 (July 17, 2007): 405–17. https://doi.org/10.1080/15374410701444363.

Knouse, Laura E., Catherine L. Bagwell, Russell A. Barkley, and Kevin R. Murphy. “Accuracy of Self-Evaluation in Adults with ADHD: Evidence from a Driving Study.” *Journal of Attention Disorders* 8, no. 4 (May 2005): 221–34. https://doi.org/10.1177/1087054705280159.

Lahey, Benjamin B., Robert F. Krueger, Paul J. Rathouz, Irwin D. Waldman, and David H. Zald. “Validity and Utility of the General Factor of Psychopathology.” *World Psychiatry* 16, no. 2 (June 2017): 142–44. https://doi.org/10.1002/wps.20410.

Lambek, Rikke, Rosemary Tannock, Soeren Dalsgaard, Anegen Trillingsgaard, Dorte Damm, and Per Hove Thomsen. “Executive Dysfunction in School-Age Children with ADHD.” *Journal of Attention Disorders* 15, no. 8 (November 2011): 646–55. https://doi.org/10.1177/1087054710370935.

Martel, Michelle M., Pedro M. Pan, Maurício S. Hoffmann, Ary Gadelha, Maria C. do Rosário, Jair J. Mari, Gisele G. Manfro, et al. “A General Psychopathology Factor (P Factor) in Children: Structural Model Analysis and External Validation through Familial Risk and Child Global Executive Function.” *Journal of Abnormal Psychology* 126, no. 1 (January 2017): 137–48. https://doi.org/10.1037/abn0000205.

Martin, Joanna, Marian L. Hamshere, Evangelia Stergiakouli, Michael C. O’Donovan, and Anita Thapar. “Genetic Risk for Attention-Deficit/Hyperactivity Disorder Contributes to

Neurodevelopmental Traits in the General Population." *Biological Psychiatry* 76, no. 8 (October 15, 2014): 664–71. https://doi.org/10.1016/j.biopsych.2014.02.013.

Moffitt, Terrie E., Renate Houts, Philip Asherson, Daniel W. Belsky, David L. Corcoran, Maggie Hammerle, HonaLee Harrington, et al. "Is Adult ADHD a Childhood-Onset Neurodevelopmental Disorder? Evidence From a Four-Decade Longitudinal Cohort Study." *American Journal of Psychiatry* 172, no. 10 (October 2015): 967–77. https://doi.org/10.1176/appi.ajp.2015.14101266.

Molina, Brooke S. G., and Margaret H. Sibley. "The Case for Including Informant Reports in the Assessment of Adulthood ADHD." *The ADHD Report* 22, no. 8 (December 1, 2014): 1–7. https://doi.org/10.1521/adhd.2014.22.8.1.

Patton, George C., Craig A. Olsson, Vegard Skirbekk, Richard Saffery, Mary E. Wlodek, Peter S. Azzopardi, Marcin Stonawski, et al. "Adolescence and the next Generation." *Nature* 554, no. 7693 (February 21, 2018): 458–66. https://doi.org/10.1038/nature25759.

Pine, Daniel S., and Nathan A. Fox. "Childhood Antecedents and Risk for Adult Mental Disorders." *Annual Review of Psychology* 66, no. 1 (January 3, 2015): 459–85. https://doi.org/10.1146/annurev-psych-010814-015038.

Pingault, Jean-Baptiste, Essi Viding, Cédric Galéra, Corina U. Greven, Yao Zheng, Robert Plomin, and Frühling Rijsdijk. "Genetic and Environmental Influences on the Developmental Course of Attention-Deficit/Hyperactivity Disorder Symptoms From Childhood to Adolescence." *JAMA Psychiatry* 72, no. 7 (July 2015): 651–58. https://doi.org/10.1001/jamapsychiatry.2015.0469.

Ratcliff, R., and G. McKoon. "A Retrieval Theory of Priming in Memory." *Psychological Review* 95, no. 3 (July 1988): 385–408.

Riglin, Lucy, Stephan Collishaw, Ajay K. Thapar, Søren Dalsgaard, Kate Langley, George Davey Smith, Evie Stergiakouli, Barbara Maughan, Michael C. O'Donovan, and Anita Thapar. "Association of Genetic Risk Variants With Attention-Deficit/Hyperactivity Disorder Trajectories in the General Population." *JAMA Psychiatry* 73, no. 12 (December 1, 2016): 1285. https://doi.org/10.1001/jamapsychiatry.2016.2817.

Salum, G. A., J. Sergeant, E. Sonuga-Barke, J. Vandekerckhove, A. Gadelha, P. M. Pan, T. S. Moriyama, et al. "Specificity of Basic Information Processing and Inhibitory Control in Attention Deficit Hyperactivity Disorder." *Psychological Medicine* 44, no. 3 (February 2014): 617–31. https://doi.org/10.1017/S0033291713000639.

Salum, G. A., E. Sonuga-Barke, J. Sergeant, J. Vandekerckhove, A. Gadelha, T. S. Moriyama, A. S. Graeff-Martins, G. G. Manfro, G. Polanczyk, and L. a. P. Rohde. "Mechanisms Underpinning Inattention and Hyperactivity: Neurocognitive Support for ADHD Dimensionality." *Psychological Medicine* 44, no. 15 (November 2014): 3189–3201.

Salum, Giovanni Abrahão, Ary Gadelha, Pedro Mario Pan, Tais Silveira Moriyama, Ana Soledade Graeff-Martins, Ana Carina Tamanaha, Pedro Alvarenga, et al. "High Risk Cohort Study for Psychiatric Disorders in Childhood: Rationale, Design, Methods and Preliminary Results: High Risk Cohort Study." *International Journal of Methods in Psychiatric Research* 24, no. 1 (March 2015): 58–73. https://doi.org/10.1002/mpr.1459.

Shevlin, Mark, Eoin McElroy, and Jamie Murphy. "Homotypic and Heterotypic Psychopathological Continuity: A Child Cohort Study." *Social Psychiatry and Psychiatric Epidemiology* 52, no. 9 (September 2017): 1135–45. https://doi.org/10.1007/s00127-017-1396-7.

Sibley, Margaret H., William E. Pelham, Brooke S. G. Molina, Elizabeth M. Gnagy, James G. Waxmonsky, Daniel A. Waschbusch, Karen J. Derefinko, et al. "When Diagnosing ADHD in Young Adults Emphasize Informant Reports, DSM Items, and Impairment." *Journal of Consulting and Clinical Psychology* 80, no. 6 (December 2012): 1052–61. https://doi.org/10.1037/a0029098.

Sibley, Margaret H., Luis A. Rohde, James M. Swanson, Lily T. Hechtman, Brooke S.G. Molina, John T. Mitchell, L. Eugene Arnold, et al. "Late-Onset ADHD Reconsidered With Comprehensive Repeated Assessments Between Ages 10 and 25." *American Journal of Psychiatry* 175, no. 2 (February 2018): 140–49. https://doi.org/10.1176/appi.ajp.2017.17030298.

Sullivan, Patrick F., Arpana Agrawal, Cynthia M. Bulik, Ole A. Andreassen, Anders D. Børglum, Gerome Breen, Sven Cichon, et al. "Psychiatric Genomics: An Update and an Agenda." *American Journal of Psychiatry* 175, no. 1 (October 3, 2017): 15–27. https://doi.org/10.1176/appi.ajp.2017.17030283.

Toplak, Maggie, and Rosemary Tannock. "Tapping and Anticipation Performance in Attention Deficit Hyperactivity Disorder." *Perceptual and Motor Skills* 100 (July 1, 2005): 659–75. https://doi.org/10.2466/PMS.100.3.659-675.

Vandierendonck, André, Eva Kemps, Maria Chiara Fastame, and Arnaud Szmalec. "Working Memory Components of the Corsi Blocks Task." *British Journal of Psychology (London,*

England: 1953) 95, no. Pt 1 (February 2004): 57–79. https://doi.org/10.1348/000712604322779460.

White, Corey N., Roger Ratcliff, Michael W. Vasey, and Gail McKoon. "Using Diffusion Models to Understand Clinical Disorders." *Journal of Mathematical Psychology* 54, no. 1 (February 1, 2010): 39–52. https://doi.org/10.1016/j.jmp.2010.01.004.

Willcutt, Erik G., Alysa E. Doyle, Joel T. Nigg, Stephen V. Faraone, and Bruce F. Pennington. "Validity of the Executive Function Theory of Attention-Deficit/Hyperactivity Disorder: A Meta-Analytic Review." *Biological Psychiatry* 57, no. 11 (June 1, 2005): 1336–46. https://doi.org/10.1016/j.biopsych.2005.02.006.

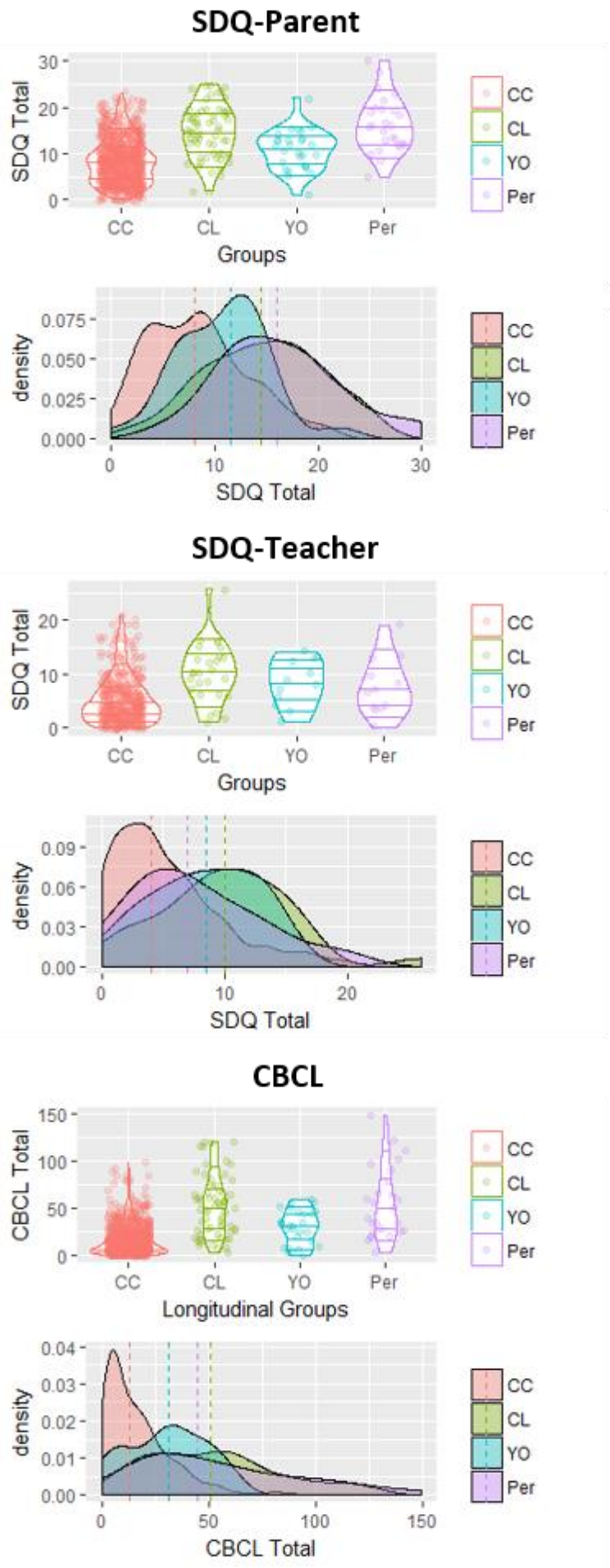
Table 1 – Sample description

	Community Comparisons n=806	Childhood-Limited n=64	Youth-Onset n=28	Persistent n=26						
	n (%) Std. Residual	n (%) Std. Residual	n (%) Std. Residual	n (%) Std. Residual	Chi-Square					
Sex (male)	428 (53.1%) -0.3	37 (57.8%) 0.4	10 (64.3%) 0.7	16 (61.5%) 0.5	x^2=2.424, p=0.489					
Ethnicity (caucasian)	490 (60.8%) -0.1	38 (59.4%) -0.2	19 (67.9%) 0.5	17 (65.4%) 0.3	x^2=0.849, p=0.838					
					YO vs. CC		YO vs. CL		YO vs. Per	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	MD	p	MD	p	MD	p
Age (baseline)	10.13 (1.06)	10.12 (1.21)	9.82 (1.06)	10.00 (1.30)	0.305	0.192	0.304	0.270	0.179	0.590
Age (follow-up)	13.56 (1.21)	13.61 (1.28)	13.14 (1.04)	13.38 (1.10)	-0.418	0.072	-0.467	0.088	-0.242	0.462
Socioeconomic scores[1]	20.33 (4.79)	20.84 (5.78)	21.36 (4.89)	21.19 (4.78)	1.030	0.271	0.513	0.642	0.165	0.901

Abbreviations: CC, Community Comparisons; CL, Childhood-Limited; YO, Youth-Onset; Per, Persistent; SD, Standard Deviation; MD, Mean Difference.

Bold font denotes statistically significant results ($p<0.05$). [1] The higher the better the socioeconomic score (ranges from 3 to 40);

Figure 1 – Violin plots and density plots comparing overall levels of baseline psychopathology among groups.



Note: Violin plots depict in points each subject score and lines representing percentiles 10, 25, 50, 75, 90 in each group. Presented analysis of parent-report SDQ and CBCL used data gathered in the baseline assessment. Questions regarding ADHD in both questionnaires were excluded. Abbreviations: CC, Community Comparison; CL, Childhood Limited; YO, Youth Onset; Per, Persistent.

Table 2 – Comorbidities and treatment

	Community Comparisons n=806	Childhood-Limited n=64	Youth-Onset n=28	Persistent n=26	
	Baseline assessment				
	n (%) Std. Residual	n (%) Std. Residual	n (%) Std. Residual	n (%) Std. Residual	Chi-Squares
Any conduct/oppositional disorder	-	20 (31.3%)	3 (10.7%)	13 (50.0%)	-
Any anxiety disorder	-	4 (6.3%)	0 (0.0%)	5 (19.2%)	-
Any depression disorder	-	7 (10.9%)	1 (3.6%)	1 (3.8%)	-
Current use of any psychiatric medication	6 (0.7%) -2.3	4 (6.3%) 2.6	0 (0.0%) -0.7	7 (26.9%) 9.4	**x^2=103.352, p<0.001**
Current use ofstimulant medication	1 (0.1%) -1.6	1 (1.6%) 1.1	0 (0.0%) -0.4	3 (11.5%) 7.6	**x^2=62.424, p<0.001**
	Follow-up assessment				
Any conduct/oppositionaldisorder	15 (1.9%) -3.9	7 (10.9%) 2.2	11 (39.4%) 8.2	12 (46.2) 9.5	**x^2=187.832, p<0.001**
Any anxiety disorder	49 (6.1%) -1.1	8 (12.5%) 1.6	6 (21.4%) 2.8	3 (11.5%) 0.8	**x^2=13.482, p=0.004**
Any depression disorder	41 (5.1%) -1.0	8 (12.5%) 2.1	2 (7.1%) 0.3	4 (15.4%) 2.0	**x^2=10.155, p=0.017**
Current use of any psychiatric medication	6 (0.7%) -1.6	0 (0.0%) -0.9	3 (10.7%) 4.2	4 (15.4%) 6.0	**x^2=57.570, p<0.001**
Current use ofstimulant medication	3 (0.4%) -0.7	0 (0.0%) -0.6	0 (0.0%) -0.4	2 (7.7%) 5.0	**x^2=25.633, p<0.001**
	Follow-up substance use assessment				
	n/available n (%) Std. Residual	n/available n (%) Std. Residual	n/available n (%) Std. Residual	n/available n (%) Std. Residual	Chi-Squares
Alcohol Use[1]	314/713 (44.0%) 0.2	21/55 (38.2%) -0.6	9/27 (33.3%) -0.8	12/21 (57.1%) 0.9	x^2=3.435, p=0.329
Tobacco Use[1]	36/718 (5.0%) -0.5	5/55 (9.1%) 1.1	3/27 (11.1%) 1.3	1/23 (4.3%) -0.2	x^2=3.402, p=0.334
IllicitDrug Use[1]	38/699 (5.4%) -0.3	3/50 (6.0%) 0.1	3/25 (12%) 1.3	1/20 (5.0%) -0.1	x^2=3.435, p=0.329

Abbreviations: CC, Community Comparisons; CL, Childhood-Limited; YO, Youth-Onset; Per, Persistent; SD, Standard Deviation; MD, Mean Difference. Bold font denotes statistically significant results (p<0.05)

[1]Not all children have complete answers in the confidential interview, number of available answers are depicted in the table and percentages are based on that specific number.

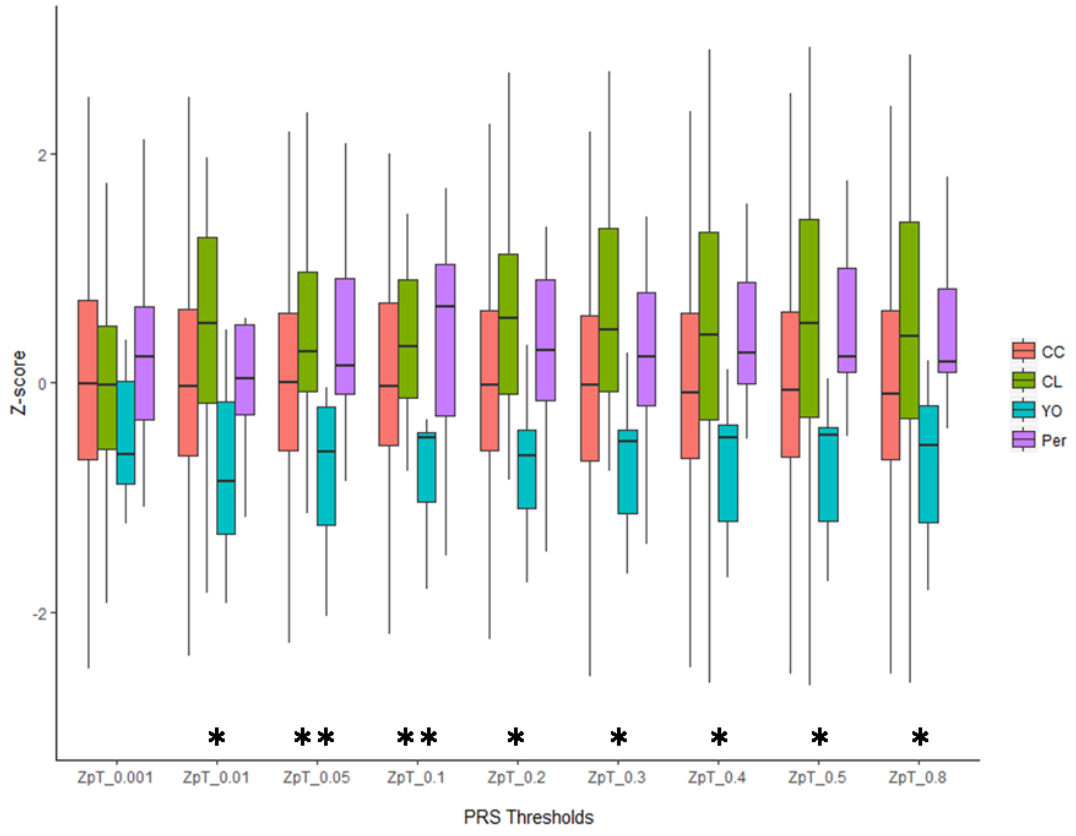
Table 3 – Cognitive assessment and school issues at baseline

	Community Comparisons n=806	Childhood-Limited n=64	Youth-Onset n=28	Persistent n=26	YO vs. CC		YO vs. CL		YO vs. Per	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	MD	p	MD	p	MD	p
IQ	101.65 (15.97)	97.28 (18.00)	96.53 (15.54)	97.66 (18.81)	-5.116	0.128	-0.747	0.849	-1.121	0.809
Executive function	0.220 (2.61)	-0.242 (2.88)	-0.943 (2.43)	-0.452 (2.32)	**-1.163**	**0.026**	-0.701	0.252	-0.491	0.499
Working memory	0.382 (4.14)	-0.943 (4.91)	-0.586 (4.38)	-0.934 (3.80)	-0.968	0.248	0.356	0.716	0.348	0.765
Inhibitory control	0.648 (8.96)	-0.372 (7.38)	-1.384 (7.13)	-0.978 (8.82)	-2.031	0.248	-1.012	0.623	-0.406	0.868
Temporal processing	0.339 (4.84)	-0.217 (5.23)	-1.964 (4.48)	-0.677 (4.36)	**-2.304**	**0.017**	-1.747	0.123	-1.287	0.339
Basic Processing										
Mean drift rate	0.321 (0.16)	0.259 (0.17)	0.256 (0.12)	0.297 (0.16)	-0.064	0.062	-0.002	0.966	-0.040	0.389
Mean non-decision time	0.241 (0.12)	0.214 (0.15)	0.209 (0.09)	0.255 (0.11)	-0.032	0.220	-0.005	0.867	-0.046	0.201
Boundary separation	0.118 (0.03)	0.128 (0.03)	0.128 (0.02)	0.117 (0.01)	0.010	0.145	-0.001	0.982	0.011	0.231
Academic performance	0.145 (0.85)	-0.523 (0.98)	-0.289 (0.95)	-0.966 (1.03)	**-0.435**	**0.009**	0.233	0.235	**0.676**	**0.004**
Sum of adverse school events	0.313 (0.77)	0.719 (1.47)	0.714 (1.18)	0.808 (1.13)	**0.402**	**0.016**	-0.004	0.982	-0.093	0.691
Reading score[1]	61.05 (12.47)	56.27 (18.03)	53.74 (12.43)	50.96 (21.61)	**-7.313**	**0.009**	-2.533	0.441	2.782	0.476
Writing score[2]	23.71 (6.77)	20.88 (8.37)	17.41 (8.85)	19.47 (7.83)	**-6.294**	**<0.001**	-3.469	0.076	-2.055	0.405
	n (%) Std. Residual	n (%) Std. Residual	n (%) Std. Residual	n (%) Std. Residual	Chi-Squares					
Adverse school events	164 (20.3%) -1.5	23 (35.9%) 2.2	10 (35.7%) 1.4	14 (53.8%) 3.3	**x^2=25.892, p<0.001**					
Repetition	142 (17.6%) -1.2	21 (32.8%) 2.4	6 (21.4%) 0.2	11 (42.3%) 2.6	**x^2=17.740, p<0.001**					
Dropout	16 (2.0%) 0.1	2 (3.1%) 0.7	0 (0.0%) -0.7	0 (0.0%) -0.7	x^2=1.543, p=0.672					
Suspension	22 (2.7%) -2.1	4 (6.3%) 0.8	8 (28.6%) 6.3	5 (19.2%) 3.7	**x^2=60.645, p<0.001**					

Abbreviations: CC, Community Comparisons; CL, Childhood-Limited; YO, Youth-Onset; Per, Persistent; SD, Standard Deviation; MD, Mean Difference.

Bold font denotes statistically significant results (p<0.05);[1]Ranges from 0-70; [2]Ranges from 0-35.

Figure 2 – Mean polygenic risk score of the longitudinal groups for multiple thresholds.



Note: Abbreviations - CC, Community Comparison; CL, Childhood-Limited; YO, Youth-Onset; Per, Persistent. * YO presented significantly lower scores than CL and Per; ** YO presented significantly lower scores than CC, CL and Per

SUPPLEMENTAL MATERIAL

Cognitive function assessment – Task descriptions

Working memory

Digit span (Vandierendonck et al., 2004).Subtest of the WISC-III consists of hearing and repeating (forwards or backward) an increasing number sequence. The level in which the child failed to repeat the numbers on two consecutive trials correctly was the outcome variable.

Corsi blocks task (Vandierendonck et al., 2004). This test involves repeating a spatial sequence tapped by a researcher on up to nine identical spatially separated blocks, with sequences that increase in length. The level in which the child failed to repeat the sequence of blocks on two consecutive trials correctly was the outcome variable.

Inhibitory control

Conflict control task (Hogan et al., 2005). In this test, children are orientated to press the button indicating the direction (congruent trial, 75 trails) or the opposite direction (incongruent trials, 25 trails) of the arrow that appears in the screen. A green arrow indicates a congruent trail and a red arrow an incongruent one. Intertrial interval was 1500ms, and stimulus duration was 100ms. The "conflict effect" of this test is based on suppressing the dominant tendency of indicating the direction of the arrow in the incongruent trials. Both accuracy and speed are equally emphasized in task instructions. The percentage of correct responses in the incongruent trial was the outcome variable.

Go/no-go (Bitsakou et al., 2008). Analogous to the CCT, in this test children are orientated to indicate the direction of the arrow that appears on the screen (75 trials)

or to suppress the stimuli entirely and do not press the button when a double-headed green arrow appeared (25 trials). As in CCT, GNG intertrial interval was 1500ms, stimulus duration was 100ms, and both accuracy and speed are emphasized in the test instructions. The percentage of failed inhibitions in the no-go trials was the dependent measure.

Time processing

Time anticipation (Toplak & Tannock, 2005). This game-like test evaluates children's capacity of anticipating when a visual stimulus would reappear by simulating a spaceship running out on oxygen. The objective of the children was to save the crew from the lack of oxygen. In each task, the spaceship would appear in the first ten trails and become invisible in the next 16 trials, when children should anticipate when the spaceship would reappear. Participants were given feedbacks after every trial. Task 1 consisted of a time interval of 750ms; task 2 consisted of a time interval of 2000ms and was always administered after the 400ms task. The mean percentage of total hits (button pressed in the correct time window interval) was the outcome measure.

Two-choice reaction time task. The 2C-RT measures the ability of the participant to perform basic decisions by orienting the participant to point the direction pointed by the arrow on the screen. As in other tasks, the intertrial interval was 1500ms, stimulus duration was 100ms, and both accuracy and speed were emphasized in the test instructions. A total of 100 arrows were presented, half pointing right and half pointing left. Reaction time and accuracy from this task were decomposed in the following parameters from diffusion models: processing efficiency (determined by the drift rate), speed-accuracy trade-off (measured as boundary separation) and encoding/motor function (measured as non-decision time).

Table 2 – Dimensional assessments

	Community Comparisons n=806	Childhood-Limited n=64	Youth-Onset n=28	Persistent n=26	YO vs. CC		YO vs. CL		YO vs. Per	
	Baseline assessment									
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	MD	p	MD	p	MD	p
Bifactor Model										
p-Factor	-0.057 (0.32)	0.719 (0.35)	0.139 (0.34)	0.833 (0.39)	**0.196**	**0.002**	**-0.580**	**<0.001**	**-0.694**	**<0.001**
Fear domain	0.005 (0.25)	0.110 (0.34)	0.057 (0.35)	-0.021 (0.43)	0.052	0.312	-0.053	0.383	0.078	0.281
Distress domain	0.009 (0.17)	0.059 (0.23)	0.035 (0.24)	-0.028 (0.28)	0.026	0.454	-0.024	0.559	0.063	0.202
Externalizing domain	-0.026 (0.32)	0.389 (0.53)	0.141 (0.50)	0.615 (0.36)	**0.167**	**0.012**	**-0.249**	**0.001**	**-0.474**	**<0.001**
DAWBA										
Inattention score	0.056 (0.26)	4.812 (2.85)	0.107 (0.42)	6.269 (2.31)	0.051	0.761	**-4.071**	**<0.001**	**-6.162**	**<0.001**
Hyperactivity score	0.072 (0.31)	6.187 (2.17)	0.107 (0.31)	7.577 (1.47)	0.035	0.790	**-6.080**	**<0.001**	**-7.470**	**<0.001**
SDQ Parent										
Total difficulties	12.24 (6.75)	22.64 (6.60)	15.75 (5.97)	25.35 (6.69)	**3.507**	**0.007**	**-6.891**	**<0.001**	**-9.596**	**<0.001**
Total score without Hyperkinetic	8.35 (4.89)	14.64 (5.65)	10.75 (4.30)	16.27 (5.91)	**2.398**	**0.012**	**-3.891**	**0.001**	**-5.519**	**<0.001**
Emotional	3.85 (2.51)	6.08 (2.72)	4.43 (2.95)	6.08 (3.07)	0.578	0.239	**-1.649**	**0.004**	**-1.648**	**0.018**
Conduct	2.29 (1.98)	4.81 (2.42)	3.50 (2.05)	5.88 (2.30)	**1.213**	**0.002**	**-1.312**	**0.004**	**-2.384**	**<0.001**
Peer Problems	2.22 (1.99)	3.75 (2.20)	2.82 (1.87)	4.31 (2.17)	0.606	0.116	**-0.929**	**0.041**	**-1.486**	**0.007**
Prosocial	8.85 (1.57)	8.06 (2.20)	8.25 (2.33)	7.38 (2.38)	-0.596	0.064	0.188	0.621	0.865	0.058
Impact	0.37 (0.84)	2.70 (2.01)	1.32 (1.66)	3.58 (2.06)	**0.954**	**<0.001**	**-1.382**	**<0.001**	**-2.225**	**<0.001**
SDQ Teacher[1]										
Total difficulties	8.45 (6.47)	15.26 (7.25)	14.25 (5.77)	14.42 (6.20)	**5.795**	**0.002**	-0.843	0.709	-0.167	0.950
Total score without Hyperkinetic	5.31 (4.45)	10.22 (5.44)	8.33 (4.27)	7.67 (5.33)	**4.914**	**<0.001**	-1.889	0.231	0.667	0.719
Emotional	2.24 (2.05)	3.96 (2.55)	3.92 (2.39)	2.25 (2.14)	**1.679**	**0.007**	-0.046	0.949	1.667	0.052
Conduct	1.41 (2.06)	3.00 (2.66)	2.83 (2.17)	3.17 (2.33)	**1.427**	**0.022**	-0.167	0.820	-0.333	0.699
Peer Problems	1.66 (1.76)	3.26 (2.03)	1.58 (1.50)	2.25 (1.71)	-0.081	0.876	**-1.676**	**0.007**	-0.667	0.358
Prosocial	7.43 (2.53)	6.15 (2.84)	8.42 (1.83)	6.58 (3.09)	0.985	0.118	**2.269**	**0.011**	1.833	0.079
Impact	0.51 (1.02)	1.19 (1.42)	1.00 (0.95)	1.17 (1.03)	0.495	0.107	-0.185	0.610	-0.167	0.697

CBCL										
Total score	20.15 (18.43)	63.45 (34.77)	36.32 (21.62)	67.12 (40.11)	**16.176**	**<0.001**	**-27.132**	**<0.001**	**-30.794**	**<0.001**
Total score without Hyperkinetic	17.07 (16.00)	52.19 (31.23)	30.14 (18.16)	55.08 (37.53)	**13.077**	**<0.001**	**-22.045**	**<0.001**	**-24.934**	**<0.001**
Internalizing	6.23 (6.35)	15.08 (10.73)	10.25 (7.35)	14.73 (12.11)	**4.023**	**0.003**	**-4.828**	**0.002**	**-4.481**	**0.019**
Externalizing	5.34 (5.89)	19.11 (11.56)	10.04 (8.38)	22.04 (14.50)	**4.699**	**<0.001**	**-9.074**	**<0.001**	**-12.003**	**<0.001**
	Follow-up assessment									
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	MD	p	MD	p	MD	p
Bifactor Model										
p-Factor	-0.203 (0.60)	0.201 (0.68)	1.369 (0.58)	1.276 (0.55)	**1.572**	**<0.001**	**1.168**	**<0.001**	0.093	0.574
Fear domain	0.012 (0.52)	0.031 (0.55)	0.087 (0.72)	0.018 (0.70)	0.075	0.465	0.056	0.644	0.070	0.631
Distress domain	0.013 (0.51)	0.057 (0.52)	-0.038 (0.59)	-0.082 (0.73)	-0.051	0.607	-0.095	0.420	0.043	0.759
Externalizing domain	-0.046 (0.60)	0.139 (0.70)	0.746 (0.69)	0.814 (0.68)	**0.792**	**<0.001**	**0.608**	**<0.001**	-0.068	0.683
DAWBA										
Inattention score	0.032 (0.19)	0.109 (0.40)	4.678 (2.64)	5.692 (2.71)	**4.646**	**<0.001**	**4.569**	**<0.001**	**-1.014**	**<0.001**
Hyperactivity score	0.088 (0.32)	0.234 (0.46)	6.786 (2.15)	7.577 (1.55)	**6.698**	**<0.001**	**6.551**	**<0.001**	**-0.791**	**<0.001**
SDQ Parent										
Total difficulties	9.91 (6.72)	14.80 (6.55)	21.21 (7.35)	23.19 (5.81)	**11.301**	**<0.001**	**6.471**	**<0.001**	-1.978	0.279
Total score without Hyperkinetic	6.92 (4.80)	9.48 (4.75)	13.57 (6.04)	14.85 (4.78)	**6.661**	**<0.001**	**4.807**	**<0.001**	-1.274	0.333
Emotional	3.14 (2.47)	3.66 (2.45)	5.29 (2.65)	5.69 (2.22)	**2.150**	**<0.001**	**1.629**	**0.004**	-0.407	0.546
Conduct	1.78 (1.92)	3.23 (2.11)	5.11 (2.66)	5.27 (2.27)	**3.328**	**<0.001**	**1.873**	**<0.001**	-0.162	0.763
Peer Problems	2.01 (1.88)	2.59 (1.97)	3.18 (2.42)	3.88 (2.42)	**1.172**	**0.002**	0.585	0.179	**-1.291**	**0.004**
Prosocial	8.56 (1.93)	8.00 (2.31)	7.39 (2.88)	7.00 (2.55)	**-1.169**	**0.003**	-0.607	0.183	0.393	0.474
Impact	0.32 (0.81)	1.00 (1.73)	3.32 (2.33)	3.42 (2.61)	**3.005**	**<0.001**	**2.321**	**<0.001**	-0.102	0.725
CBCL										
Total score	26.34 (96.42)	40.66 (27.49)	67.54 (28.83)	69.04 (36.35)	**41.200**	**0.018**	26.879	0.192	-1.503	0.952
Total score without Hyperkinetic	23.39 (95.98)	33.72 (23.08)	55.64 (25.61)	57.12 (33.12)	32.252	0.063	21.924	0.284	-1.473	0.952
Internalizing	9.45 (27.29)	11.69 (9.81)	17.32 (11.36)	18.15 (11.34)	7.873	0.113	5.634	0.335	-0.832	0.906
Externalizing	7.83 (42.25)	12.22 (9.25)	21.89 (12.07)	22.35 (13.39)	14.065	0.066	9.674	0.282	-0.453	0.967

Abbreviations: CC, Community Comparisons; CL, Childhood-Limited; YO, Youth-Onset; Per, Persistent; SD, Standard Deviation; MD, Mean Difference.

Bold font denotes statistically significant results (p<0.05)

[1]Not all children had SDQ teacher reports, this analysis is comprised of 447 participants (396 CC, 27 CL, 12 YO and 12 Per).

Supplemental Table S2 - Dimensional assessment in baseline by CBCL quartiles

	Community Comparisons	Childhood-Limited	Youth-Onset	Persistent	
Quartiles	n (%) Std. Residual	n (%) Std. Residual	n (%) Std. Residual	n (%) Std. Residual	Chi-Squares
CBCL Total					
<25%	238 (29.5%) 1.9	1 (1.6%) -3.8	3 (10.7%) -1.6	0 (0.0%) -2.6	
25-50%	214 (26.6%) 1.4	3 (4.7%) -3.2	4 (14.3%) -1.1	2 (7.7%) -1.7	**x^2=166.883, p<0.001**
50-75%	210 (26.1%) 0.6	12 (18.8%) -1.0	4 (14.3%) -1.1	5 (19.2%) -0.6	
>75%	144 (17.9%) -3.9	48 (75.0%) 8.1	17 (60.7%) 3.8	19 (73.1%) 5.0	
CBCL Total without Hyper					
<25%	239 (29.7%) 1.8	1 (1.6%) -3.9	3 (10.7%) -1.6	1 (3.8%) -2.2	
25-50%	223 (27.7%) 1.3	5 (7.8%) -2.8	5 (17.9%) -0.8	1 (3.8%) -2.2	**x^2=136.965, p<0.001**
50-75%	200 (24.8%) 0.2	14 (21.9%) -0.4	5 (17.9%) -0.7	7 (26.9%) 0.3	
>75%	144 (17.9%) -3.5	44 (68.8%) 7.4	15 (53.6%) 3.2	17 (65.4%) 4.3	
CBCL Internalizing					
<25%	273 (33.9%) 1.5	6 (9.4%) -3.1	5 (17.9%) -1.2	1 (3.8%) -2.5	
25-50%	193 (23.9%) 0.7	7 (10.9%) -2.0	5 (17.9%) -0.5	5 (19.2%) -0.4	**x^2=97.485, p<0.001**
50-75%	188 (23.3%) 0.5	10 (15.6%) -1.2	3 (10.7%) -1.3	7 (26.9%) 0.5	
>75%	152 (18.9%) -2.9	41 (64.1%) 6.6	15 (53.6%) 3.2	13 (50.0%) 2.7	
CBCL Externalizing					
<25%	232 (28.8%) 1.6	2 (3.1%) -3.6	5 (17.9%) -0.8	0 (0.0%) -2.6	
25-50%	243 (30.1%) 1.4	5 (7.8%) -3.0	5 (17.9%) -1.0	1 (3.8%) -2.3	**x^2=176.093, p<0.001**
50-75%	201 (24.9%) 0.7	9 (14.1%) -1.6	5 (17.9%) -0.6	5 (19.2%) -0.5	
>75%	130 (16.1%) -4.0	48 (75.0%) 8.7	13 (46.6%) 2.6	20 (76.9%) 5.8	

Abbreviations: CC, Community Comparisons; CL, Childhood-Limited; YO, Youth-Onset; Per, Persistent; Std, Standard;
Bold font denotes statistically significant results (p<0.05)

Table S3 – Logistic regressions prediction models

Persistence				
	Univariate		Multiple	
	OR	p	OR	p
Sex/Gender (male)	1.168	0.745	0.849	0.788
Age	0.926	0.673	0.967	0.892
Socioeconomic (score)	1.012	0.784	1.053	0.409
IQ (score)	1.001	0.931	1.004	0.799
Comorbid Conduct	2.200	0.098	2.540	0.144
Comorbid Depression	0.326	0.306	0.089	0.051
Comorbid Anxiety	3.571	0.076	5.291	0.063
Executive Function	0.971	0.739	0.943	0.615
Total of Symptoms in Baseline	**1.315**	**0.001**	**1.368**	**0.001**
Family Risk for ADHD	0.358	0.352	0.348	0.463
Incidence	OR	p	OR	p
Sex/Gender (male)	1.590	0.247	1.669	0.245
Age	0.809	0.191	0.825	0.294
Socioeconomic (score)	1.044	0.263	**1.111**	**0.016**
IQ	0.979	0.123	0.985	0.316
Comorbid Conduct	-	-	-	-
Comorbid Depression	-	-	-	-
Comorbid Anxiety	-	-	-	-
Executive Function	**0.847**	**0.027**	**0.824**	**0.030**
Total of Symptoms in Baseline	1.451	0.297	1.262	0.561
Family Risk for ADHD	1.795	0.528	1.814	0.562

Abbreviations: OR, Odds ratio; IQ, Intelligence Quotient; ADHD, Attention-deficit/hyperactivity Disorder.

Boldfont denotes statisticallysignificantresults ($p<0.05$).

Sensitivity analysis – 11-12 years old baseline subsample

Sensitivity analysis was performed with a subsample of 11-12 years old at baseline to increase the probability of ADHD incidence disrespect age of onset as determined by DSM-5. A subsample of 178 individuals (154 CC, 11 CL, 7 YO and 6 Per) was evaluated re-analyzing all comparisons done in the original sample, including sample description, comorbidities, cognitive & school assessments and dimensional assessments (total of 163 comparisons). Teacher-reports and genetic correlates, however, could not be analyzed due to small sample sizes. Results from the subsample were compared to the original sample and divided into four categories: (1) confirmed results, (2) convergent results with a loss of statistical significance, (3) convergent results with a gain of statistical significance and (4) divergent results. Almost all of the comparisons kept convergent (97%), with a large number of confirmed results (59%). Results are described below and tables informing the number of confirmed analyses are depicted for both cognitive & school assessments and dimensional assessments. Complete data on all analysis are available upon request.

In sample description analysis all but one result were confirmed. YO was found to be older than Per cases. For the comorbidities and treatment analysis, all but one result were also confirmed. There was a loss of significance and a smaller prevalence of depression at follow-up for CL and YO cases. Results from cognitive and dimensional assessments are presented in Tables S4 and S5, with most of the results confirmed. Divergent results consisted of worse working memory and higher sum of adverse school events of YO when compared to CL; and a loss of significance in peer problems comparing YO to Per.

Supplemental Table S4 –Sensitivity analysis for cognitive and school assessment

	YO vs. CC	YO vs. CL	YO vs. Per
Number of confirmed results	7	8	10
Number of convergent results that lost statistical significance	3	0	0
Number of convergent results that gained statistical significance	2	2	2
Number of divergent results	0	2	0

Notes: a result was considered to be confirmed in two conditions – if it was originally statistically significant and kept both significance and directionality and if it was originally statistically insignificant and kept its insignificance.

Supplemental Table S5 – Sensitivity analysis for dimensional assessment

	YO vs. CC	YO vs. CL	YO vs. Per
Number of confirmed results	21	13	20
Number of convergent results that lost statistical significance	10	6	12
Number of convergent results that gained statistical significance	3	5	1
Number of divergent results	0	0	1

Notes: a result was considered to be confirmed in two conditions – if it was originally statistically significant and kept both significance and directionality and if it was originally statistically insignificant and kept its insignificance.

4. ARTIGO #2

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Testing the Stability and Validity of an Executive Dysfunction Class using Task-Based Assessment in Children and Adolescents.

Running Title: Task-Based Executive Dysfunction Class

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ABSTRACT

Objective: It is unclear if pediatric executive dysfunction, assessed only with cognitive-tasks, predicts clinically-relevant outcomes independently of psychiatric diagnoses. This study tests the stability and validity of a task-based classification of executive function.

Method: A total of 2,207 participants (6-17 years old) from the Brazilian High-Risk Cohort Study participated in this study (1,930 at baseline; 1,532 at follow-up). Executive function was measured using tests of working memory and inhibitory control. Dichotomized age- and sex-standardized performances were used as input in a Latent Class Analysis and Receiver Operating Curves to create an Executive Dysfunction Class (EDC). The study tests EDC's stability over time, association with symptoms, functional impairment, a polymorphism in the CADM2 gene, polygenic risk scores (PRS), and brain structure. Analyses covaried for age, sex, social class, intelligence quotient, and psychiatric diagnoses.

Results: EDC at baseline predicted itself at follow-up (OR=5.11, CI 95% 3.41-7.64). Participants in the EDC reported symptoms spanning several domains of psychopathology and exhibited impairment in multiple settings, including more adverse school events (OR=2.530, CI95% 1.838-3.483). Children in the EDC presented higher ADHD and lower educational attainment PRS at baseline, higher schizophrenia PRS at follow-up and lower chances of presenting a polymorphism in a gene previously linked to high performance in executive function (CADM2 gene). They also exhibited smaller intracranial volumes and smaller bilateral cortical surface areas in several brain regions.

Conclusion: Task-based executive dysfunction is associated with several validators, independently of psychiatric diagnoses and intelligence. Further refinement of task-based assessments might generate clinically useful tools.

Key-Words: Executive Function; RDoC; Neuropsychology; Genetics; Neuroimage

INTRODUCTION

Current definitions of mental disorders primarily rely on behavioral observations and symptom reports [1]. Ongoing initiatives, such as Research Domain Criteria (RDoC) [2], seek to integrate task-performance measures into these definitions. With this approach, task-based measures might connect clinical assessments to neuroscientific understandings in ways that inform pathophysiology [3] and increase objectivity in current classification schemes [4], [5]. The validity of task-based classification can be evaluated through research on external correlates such as relations functional impairment, established genetic factors for psychopathology, and brain structure, while adjusting for the effects of current diagnostic categories. The current study extends preliminary work in pediatric psychopathology by examining associations among task-based assessments of executive function, symptom reports, and external validators.

This study uses tasks for a well-established construct: Executive Function (EF). EF encompasses high-level cognitive skills needed to plan and perform goal-directed behaviors [6]. While different models of EF exist, most definitions include domains of working memory and inhibitory control [7]–[10]. EF deficits relate to overall levels of psychopathology [11] and occur in most psychiatric disorders [12]–[15]; the deficits also predict adverse outcomes [16], [17]. While EF testing possesses some clinical utility and validity [18], most work on EF has examined its relationship to specific disorders [19], [20]. Much of this research examines pediatric samples, given the relevance of EF for neurodevelopmental disorders. Few comprehensive studies evaluate the utility of EF in classification. Available work typically combines data from EF tests and symptom

reports, despite low correlations between the two sets of measures. Therefore, the utility of stand-alone task-based EF classification in youth remains insufficiently evaluated. Work is needed on evaluating associations with functional outcomes and biological correlates, independent of socioeconomic factors, intelligence, and concurrent psychopathology.

The current study proceeds in three stages to define and validate a profile of EF impairment. First, the study uses measures of working memory and inhibitory control to identify youth with impaired executive function – defined as the Executive Dysfunction Class (EDC) [21]. Next, the study examines associations among this EDC class with symptom-based measures of psychopathology, and clinically-meaningful longitudinal outcomes. Finally, the study examines relationships with genetic and brain structural variables. All analyses adjust for age, sex, socioeconomic status, and psychiatric diagnoses. Through these stages, this study tests the hypothesis that youth in the EDC will manifest impaired function, associated psychopathology, genetic risk indicators, and differences in brain structure. Using EDC as an example, we aim to test if operationalized task-based classifications can add information above and beyond our symptom-based current diagnostic categories.

METHODS AND MATERIALS

Sample Description

The Brazilian High-Risk Study for Psychiatric Disorders (BHRCS) is a large school-based community cohort from two Brazilian cities: Porto Alegre and São Paulo. The 2,511 children and adolescents who participated in the study (1,554 high-risk for psychiatric disorders, identified using current symptoms and family history, and 957 randomly selected) were thoroughly assessed with psychiatric instruments and neurocognitive tests. A subsample of 2,185 participants were genotyped and 741 individuals were assessed with imaging protocols. Follow-up interviews were conducted on average 3 years later, with a retention rate of 80%. The study was approved by the ethical committee of the University of Sao Paulo. Informed consent was obtained from the parents of all participants. Further information on the BHRCS can be found elsewhere [22].

Inclusion and Exclusion Criteria

Our study sample is composed of all participants who had complete information on age, neuropsychological tests, and IQ. We excluded participants with IQ<70 to avoid biases regarding intellectual deficiency. A total 1,930 (6-14 years-old, 54.7% male) subjects were analyzed at baseline and 1,531 (9-17 years-old, 55.8% male) were evaluated at follow-up. The analyzed sample was not statistically distinct from the full BHRCS on age, sex, socioeconomic score, presence of any psychiatric diagnosis or level of psychopathology (all $p>0.05$).

Executive Function Assessment

We assessed EF using cognitive tests conducted by trained mental health professionals. The two constructs of executive function assessed in our study are working memory and inhibitory control. The following tasks were used to measure these constructs at baseline and follow-up.

Working memory

Digit span task [23]. This subtest of the WISC-III consists of hearing and repeating an increasing number sequence, either as heard (forward) or in reverse order (backward). The level at which the child failed to repeat the numbers on two consecutive trials in the backwards condition correctly was the outcome variable.

Corsi blocks task (Corsi) [24]. This test involves repeating a spatial sequence on up to nine identical spatially separated blocks. The sequences are tapped by a researcher and increase in length, either as showed by the examiner (forward) or in reverse order (backward). The level at which the child failed to repeat the sequence of blocks on two consecutive trials in the backwards condition correctly was the outcome variable.

Inhibitory control

Conflict control task (CCT) [25]. In this test, children are instructed to press a button indicating the direction (congruent trial, 75 trials) or the opposite direction (incongruent trials, 25 trails) of the arrow that appears on the screen. A green arrow indicates a congruent trail and a red arrow an incongruent one. Intertrial interval was 1500ms, and stimulus duration was 100ms. The “conflict effect” of this test is based on suppressing the dominant tendency of indicating the direction of the arrow in the incongruent trials. Both accuracy and speed are equally emphasized in task instructions. The percentage of correct responses in the incongruent trial was the outcome variable.

Go/no-go (GNG) [26]. Analogous to the CCT, in this test children are instructed to indicate the direction of the arrow that appears on the screen (75 trials) or to suppress the stimuli entirely and do not press the button when a double-headed green arrow appears (25 trials). Intertrial interval was 1500ms, stimulus duration was 100ms, and both accuracy and speed are emphasized in the test instructions. The percentage of failed inhibitions in the no-go trials was the dependent measure.

Operationalization of EDC

This study performed a sequential three-step approach to operationalize the EDC. We used multiple tasks instead of one task because we assumed that each task is an incomplete indicator of the EF construct. Aggregating information from distinct sources of variance is likely to improve our phenotypic characterization and stability of the classification. The following three-step classification procedure was used to operationalize the EDC at both baseline and follow-up assessments.

Test Result Threshold: we first investigated the distribution of each test result in only the random sample of the BHRCS (n=957), thus generating normative performance tables for each age-group and sex. Then, we dichotomized the performance of all subjects of the sample (high-risk and random) into low-performance (defined as at or below the 10^{th} percentile of the reference population) vs. normal/high-performance, adjusting for sex and age). The 10^{th} percentile threshold was selected a priori because it has been used to stratify performance in previous studies [13]. At the end of this step each subject had a dichotomous result for each of the four tests.

Classification Threshold: using the individual indicators of low vs normal/high test performance in each test as input, we performed a data-driven analysis to find a

cluster of subjects with the lowest test performance globally. This analysis was performed using a Latent Class Analysis (LCA). At the end of this step each subject was classified as being a class member of a global low-performance cluster or not.

Clinical Translation: as it would be unfeasible for a clinician in a real world setting to perform an LCA to assign class membership for individual patients, we used ROC curves to determine the number of low-performance test results needed to best identify the low-performance cluster of subjects defined by the LCA (considered as the "gold-standard"). The optimal cut-off for ROC analyses was estimated using the Younden's J Statistic, which maximizes both sensitivity and specificity [27]. This last step was used so EDC could be determined using simply the number of low-performance tests and therefore be applicable in clinical settings.

Validators

Symptom-level analysis & Categorical Diagnoses

We used the Brazilian version of the Child Behavior Checklist (CBCL) [28] to investigate dimensional psychopathology. The CBCL is 121-item questionnaire that provides information on several domains of dimensional psychopathology including anxious/depressed, withdrawal/depressed, aggressive behavior, attention difficulties, rule-breaking behavior, social problems, somatic complains, thought problems and others [29], [30].

Categorical diagnoses of the main child-adolescent psychiatric higher-order groups (Any Anxiety Disorder, Any Depressive Disorder, Any Attention-Deficit/Hyperactivity Disorder and Any Disruptive Behavior Disorder) were performed by the Development and Well-Being Assessment (DAWBA) administered by trained lay-

interviews and answered by the subject's parents at baseline. At follow-up, the DAWBA was also administered by trained psychologists to children and adolescents for internalizing modules with the final diagnosis being made by a psychiatrist using the best estimate procedure from the two separate interviews [31].

Impact on functioning

We evaluated impact on different settings (education, family life and friendships). For all these settings, the impact was initially measured using the SDQ impact module, answered by the participant's parents and teachers [32], [33]. In this section of the questionnaire, parents and teachers were asked to what degree the child's difficulties interfere with the evaluated areas, classified as: "not at all", "only a little", "a medium amount", or "a great deal". We considered impairment to be present if difficulties interfered at least "a medium amount". Teacher reports were available for a subsample of 1189 participants at baseline.

Education. Categorical adverse school events (repetition, dropout, suspension and expulsion) were directly asked to the subjects' parents. A composite dimensional score containing those items was called "non-attendance"; in addition, a categorical variable denoting the occurrence of "Any Negative School Event" was constructed. School achievement was assessed using the school items of the CBCL, where participants were scored regarding their performance in academic subjects (Portuguese or literature, history or social studies, English or Spanish, mathematics, biology, sciences, geography, and computer studies). Reading and writing abilities were evaluated using subtests of the Brazilian School Performance Test [34]. A composite score of reading and writing ability ("literacy") was constructed. The composite scores described above were

calculated using the original variables, in a unidimensional Confirmatory Factor Analysis (CFA). Individual standardized factor scores were estimated adjusting for the effects of sex and age.

Polygenic Risk Scores

DNA was extracted from blood and genotyping was performed using the Global Screening Array (Illumina). The study evaluates associations with specific polymorphisms of the *CADM2* gene (rs17518584), previously associated with executive functioning in genome wide arrays [35]. In our study, we investigated the additive, dominant and recessive models of this SNP which was imputed based on a highly liked polymorphism rs10865610 (r2=0.96). Also, the study examined associations between EDC and polygenic risk scores (PRS) for specific constructs, including ADHD [36], education attainment [37], major depression [38], and schizophrenia [39]. The Cross-Disorder PRS [40], which includes shared genetic variance for autism spectrum disorder, ADHD, bipolar disorder, major depressive disorder, and schizophrenia, was also investigated. Polygenic risk scores were calculated using the PRSice v2 software [41]. All associated SNPs were included in the analysis, without setting any threshold. PRS were transformed into z scores to facilitate interpretation, and analyses were adjusted for the first 10 principal components of ancestry. Genetic analyses were available for 1821 participants at baseline and 1416 participants at follow-up.

Neuroimaging

MRI scans were performed at two sites, using 1.5T scanners (GE Signa HDX and GE Signa HD; GE, USA) running identical imaging protocols. Structural neuroimage

variables included total intracranial volumes (ICV), total cortical thickness, and total cortical surface area bilaterally. Images from the structural sequences were processed using FreeSurfer, version 6.0 [42] and a visual inspection quality control was performed that led to the exclusion of 82 scans. We performed a stepwise analysis. First, we investigated global measures of area, thickness and volume. If global measures were significant, we further explored specific parcellations provided by the Desikan-Killany cortical atlas. Neuroimage analyses were also controlled for site. MRI scans were available for a random subsample of 547 participants at baseline and 359 participants at follow-up.

Covariates

Categorical psychiatric diagnoses were assessed as previously described. The study measured IQ at baseline using vocabulary and block design subtests of the Weschler Intelligence Scale for Children, third edition (WISC-III) [23]. Socioeconomic status was measured using the Brazilian Economic Classification Criteria, which considers the family's possessions and educational status [43].

Statistical Analysis

Temporal Stability

We tested temporal stability of EDC by assessing longitudinal patterns of incidence, remission and persistence of the classification at baseline and follow-up assessments. Also, we calculated the odds of the individual having EDC at follow-up based on its status at the baseline.

Validity

All analyses were performed using generalized additive mixed models to account for non-linearities between age and the measured outcomes, using site (Porto Alegre or São Paulo) as random intercepts, and adjusting for sex, SES, IQ, any anxiety disorder, any depressive disorder, any ADHD and any conduct disorder. For neuroimaging analysis, we fitted separate age splines for sex, given well known distinctions in the trajectories of brain volumes between boys and girls. Symptomatic and neuroimaging analysis were corrected using false discovery rate due to a high number of statistical tests. Longitudinal analysis was also repeated using an imputation method of Chain Equations [44], to account for differential loss to follow-up. All analyses were conducted in R 3.6.1 [45], using the applications from the following packages: poLCA 1.4.1 [46] for performing of the LCAs; pROC 1.15.3 [47] for assessing the ROC curves, gamm4 0.2.5 [48] for performing generalized addictive mixed-models and MICE for imputation [49].

RESULTS

As a descriptive assessment, we show correlation matrices between both task-based performance and symptom-based performance. EF and CBCL-based variables segregated into two minimally-overlapping clusters (Figure 1).

Operationalization

Data were examined using a 10^{th}-percentile threshold for each test, adjusted for age and sex (see Supplemental Material, Table S1). The LCA found the 2-class distribution (low vs normal/high performance) as the best solution, with ROC analysis suggesting an optimal threshold for identifying EF dysfunction as ≥2 low-performance tests. Using this cut-off, at both baseline and follow-up, AUC was > 0.98, sensitivity was = 1.00, and specificity was > 0.95. Full information on the operationalization appears in supplemental material. Table S2 provides the sample description.

Stability over time

From the 1,364 individuals with full EDC information at baseline and follow-up, longitudinal trajectories comprised: 1088 controls (79.8%), 159 remittent cases (11.7%), 67 incident cases (4.9%), and 50 persistent cases (3.7%). From those 117 participants with EDC at follow-up, 50 (43.7%) were already classified as EDC at baseline. From those 1,155 not classified as EDC at baseline, incidence occurred in 67 (5.8%). EDC at baseline increased the odds of follow-up EDC by 5 times (OR=5.11, CI 95% 3.41 – 7.64, AUC=0.750).

Validity

Symptom-level Regressions & Categorical Diagnoses

At baseline, seven CBCL items were statistically associated with EDC after correction for multiple comparisons: “poor school work”, “easily embarrassed”, “gets teased a lot”, “too shy or timid”, “physical problems without known medical cause”, “daydreams or gets lost in his/her thoughts”, and “complains of loneliness”. At follow-up, three items were statistically significant: “acts too young for his/her age”, “poor school work”, and “has strange ideas”. Associations spanned almost all domains of psychopathology as can be seen in Figure 2. EDC was not associated with categorical diagnoses of mental disorders at baseline or follow-up, when analyses were conducted correcting for comorbidity including all but the tested disorder (Table S3).

Functional Impairment

Participants with EDC presented worse scores on non-attendance, school achievement and literacy, as well as a higher frequency of adverse school events on both baseline and follow-up. Worse school attendance and achievement on follow-up were predicted by baseline EDC status even adjusting for the presence of those impairments at baseline. Impairment on family life and friendships was seen with less consistency. Results are depicted in Table 1. No longitudinal results were modified when analyzed using imputation techniques (Table S4).

Genetic analysis

Under a dominant model, the TT genotype at rs17518584 was nominally associated with EDC at follow-up (OR = 0.632, CI95% 0.397-0.991, p=0.046). No associations were found for the additive or recessive models. Participants with EDC had

higher ADHD PRS and lower educational attainment PRS at baseline and higher schizophrenia PRS at follow-up (Table 2).

Neuroimaging

Children in the EDC presented with lower cortical surface areas bilaterally, with no significant associations observed for cortical thickness or volume of subcortical structures (Table 2). Given significant associations with global cortical areas, we further explored the 68 area parcellations correcting for multiple comparisons (Figure 3, Table S5). At baseline, lower cuneus area was observed in right hemisphere (SMD=-0.371, p_{adj}=0.047), and lower superior parietal areas were seen bilaterally (right - SMD=-0.375, p_{adj} =0.047; left - SMD=-0.439, p_{adj}=0.033). At follow-up, superior temporal (SMD=-0.462, p_{adj}=0.036), banks superior temporal (SMD=-0.504, p_{adj}=0.032), cuneus (SMD=-0.477, p_{adj}=0.032), and pars triangularis (SMD=-0.486, p_{adj}=0.032) were observed in the right hemisphere; again, lower superior parietal areas were seen bilaterally (right - SMD=-0.529, p_{adj}=0.036; left - SMD=-0.492, p_{adj}=0.032).

Supplemental analysis

The EDC operationalized by the four EF tests and LCA-based solution was more stable and more consistently associated with external correlates than each task taken individually (Table S6).

DISCUSSION

This study evaluated the stability and validity of task-based approaches of classification, using deficits in executive function (EDC) as an example of a clinically useful group. The results suggest that a threshold of ≥2 low-performance scores among 4 objective neuropsychological tests identifies a meaningful group of low-performing youth. EDC caseness predicted itself over time, predicted symptoms related to several domains of psychopathology and adverse impacts on learning both concurrently and over time. Educational impairments included lower academic performance and a substantial higher frequency of adverse school events. Moreover, caseness also predicted profiles on genetic and neuroimaging external correlates, with all such findings emerging independent of existing psychiatric disorder classification and IQ. Thus, further refinement of task-based assessments for use in children and adolescents might generate clinically useful information.

The potential utility of data-driven classification [50], [51] has been shown through several studies [52]–[57], including several investigations examining executive function. The current study builds up on previous data-driven literature that showed executive function deficits to be transdiagnostic [58], [59]. For example, Ing and collaborators, found specific functional neuroimaging correlates of EF deficits [56]. Such findings extend other work linking EF deficits to modifications in brain function that manifest across current psychiatric classifications [60], [61]. However, whereas past research provides a framework for continued studies of EF deficits, previously used cluster-based methods do not easily extend previous research on pediatric psychopathology. This occurs given the lack of comparability and standardization across studies, which is particularly important among youth, given age-related changes in EF.

Ultimately, classification serves functions beyond informing studies of pathophysiology; it also predictively informs patients and clinicians on the likely occurrence of functional impairment and the prognosis for the patient. Our study addresses each such aspect of classification. The data suggest that (a) EF deficits can be recognized in community samples using simple tests; (b) operationalization of a classification is feasible, in a way that (c) possesses utility and validity independent of current symptom-based classification.

By showing that such classifications bring objectivity to psychiatric assessment without losing the capacity to detect children with unfavorable outcomes, we open the possibility to further advance this approach to other phenotypes and for investigation of fine tune interventions to more specific domains. For example, despite focusing on current diagnostic groups, EF interventions [62]–[66] could focus more specifically in children likely to have EF impairments and that already carry significant risks of an atypical development such as the ones captured by the EDC.

Limitations of the study should be noted. First, we based the construction of the EDC on working memory and inhibitory control, but not in cognitive flexibility or other components of EF. Even though the executive function domains often converge, it could be argued that the absence of cognitive flexibility measures yields an incomplete assessment of EF. However, working memory and inhibitory control are basic EF domains that support high-order EF, which are known to be reliably testable [18] and with the potential for intervention [62], [66]–[69]. Second, the analysis was limited to one cohort, and, as such, replication in independent samples is essential. Third, by categorizing our executive function outcomes, we may lose some information. Nevertheless, this strategy enables the EDC to be used in clinical settings, where

dichotomization is often required. The study has important strengths. First, we used simple and well-validated tests to build our operationalization. This testing is possible in real-world settings, such as primary care and clinical offices. Second, we validated our phenotype on matters of symptomatology, impairment, and biological variables. Third, by controlling for psychiatric comorbidities and IQ, we were able to validate EDC independently of our current classificatory system. Lastly, we demonstrated that task-based measures can predict clinically relevant outcomes over a three-year period, over and above symptomatology rating measures.

This study demonstrates the potential value of operationalized criteria using a task-based classification. Such strategy, based on objective evaluations, identifies neurobiological underpinnings and associated impairments that might be currently diluted throughout several psychiatric disorders. Thus, it might (a) facilitate communication in research and clinical practice; (b) augment existing symptom-based assessment; and (c) inform research on therapeutics. Operationalization of task-based classifications may play a role in translating research efforts into clinical practice.

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REFERENCES

[1] American Psychiatric Association, *Diagnostic and statistical manual of mental disorders - 5th edition.* 2013.

[2] T. Insel *et al.*, "Research Domain Criteria (RDoC): Toward a New Classification Framework for Research on Mental Disorders," *AJP*, vol. 167, no. 7, pp. 748–751, Jul. 2010, doi: 10.1176/appi.ajp.2010.09091379.

[3] G. A. Salum, A. Gadelha, G. V. Polanczyk, E. C. Miguel, and L. A. Rohde, "Diagnostic operationalization and phenomenological heterogeneity in psychiatry: the case of attention deficit hyperactivity disorder," *Salud Mental*, vol. 41, no. 6, pp. 249–259, Dec. 2018, doi: 10.17711/SM.0185-3325.2018.037.

[4] S. Kapur, A. G. Phillips, and T. R. Insel, "Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it?," *Mol. Psychiatry*, vol. 17, no. 12, pp. 1174–1179, Dec. 2012, doi: 10.1038/mp.2012.105.

[5] M. P. Milham, R. C. Craddock, and A. Klein, "Clinically useful brain imaging for neuropsychiatry: How can we get there?," *Depress Anxiety*, vol. 34, no. 7, pp. 578–587, 2017, doi: 10.1002/da.22627.

[6] P. Anderson, "Assessment and development of executive function (EF) during childhood," *Child Neuropsychol*, vol. 8, no. 2, pp. 71–82, Jun. 2002, doi: 10.1076/chin.8.2.71.8724.

[7] M. R. Rueda, M. I. Posner, and M. K. Rothbart, "The Development of Executive Attention: Contributions to the Emergence of Self-Regulation," *Developmental Neuropsychology*, vol. 28, no. 2, pp. 573–594, Oct. 2005, doi: 10.1207/s15326942dn2802_2.

[8] W. Hofmann, B. J. Schmeichel, and A. D. Baddeley, "Executive functions and self-regulation," *Trends in Cognitive Sciences*, vol. 16, no. 3, pp. 174–180, Mar. 2012, doi: 10.1016/j.tics.2012.01.006.

[9] M. D. Lezak, "The Problem of Assessing Executive Functions," *International Journal of Psychology*, vol. 17, no. 1–4, pp. 281–297, 1982, doi: 10.1080/00207598208247445.

[10] A. Miyake and N. P. Friedman, "The Nature and Organization of Individual Differences in Executive Functions: Four General Conclusions," *Curr Dir Psychol Sci*, vol. 21, no. 1, pp. 8–14, Feb. 2012, doi: 10.1177/0963721411429458.

[11] S. Shanmugan *et al.*, “Common and Dissociable Mechanisms of Executive System Dysfunction Across Psychiatric Disorders in Youth,” *Am J Psychiatry*, vol. 173, no. 5, pp. 517–526, 01 2016, doi: 10.1176/appi.ajp.2015.15060725.

[12] J. Biederman *et al.*, “Impact of executive function deficits and attention-deficit/hyperactivity disorder (ADHD) on academic outcomes in children,” *J Consult Clin Psychol*, vol. 72, no. 5, pp. 757–766, Oct. 2004, doi: 10.1037/0022-006X.72.5.757.

[13] J. T. Nigg, E. G. Willcutt, A. E. Doyle, and E. J. S. Sonuga-Barke, “Causal heterogeneity in attention-deficit/hyperactivity disorder: do we need neuropsychologically impaired subtypes?,” *Biol. Psychiatry*, vol. 57, no. 11, pp. 1224–1230, Jun. 2005, doi: 10.1016/j.biopsych.2004.08.025.

[14] B. F. Pennington and S. Ozonoff, “Executive functions and developmental psychopathology,” *J Child Psychol Psychiatry*, vol. 37, no. 1, pp. 51–87, Jan. 1996, doi: 10.1111/j.1469-7610.1996.tb01380.x.

[15] N. F. Forbes, L. A. Carrick, A. M. McIntosh, and S. M. Lawrie, “Working memory in schizophrenia: a meta-analysis,” *Psychol Med*, vol. 39, no. 6, pp. 889–905, Jun. 2009, doi: 10.1017/S0033291708004558.

[16] R. Loeber *et al.*, “Findings From the Pittsburgh Youth Study: Cognitive Impulsivity and Intelligence as Predictors of the Age–Crime Curve,” *Journal of the American Academy of Child & Adolescent Psychiatry*, vol. 51, no. 11, pp. 1136–1149, Nov. 2012, doi: 10.1016/j.jaac.2012.08.019.

[17] T. E. Moffitt *et al.*, “A gradient of childhood self-control predicts health, wealth, and public safety,” *Proc. Natl. Acad. Sci. U.S.A.*, vol. 108, no. 7, pp. 2693–2698, Feb. 2011, doi: 10.1073/pnas.1010076108.

[18] R. C. K. Chan, D. Shum, T. Toulopoulou, and E. Y. H. Chen, “Assessment of executive functions: review of instruments and identification of critical issues,” *Arch Clin Neuropsychol*, vol. 23, no. 2, pp. 201–216, Mar. 2008, doi: 10.1016/j.acn.2007.08.010.

[19] T. E. Moffitt and B. Henry, “Neuropsychological assessment of executive functions in self-reported delinquents,” *Development and Psychopathology*, vol. 1, no. 2, pp. 105–118, Apr. 1989, doi: 10.1017/S0954579400000298.

[20] T. E. Moffitt, “The neuropsychology of conduct disorder,” *Development and Psychopathology*, vol. 5, no. 1–2, pp. 135–151, ed 1993, doi: 10.1017/S0954579400004302.

[21] E. Robins and S. B. Guze, “Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia,” *Am J Psychiatry*, vol. 126, no. 7, pp. 983–987, Jan. 1970, doi: 10.1176/ajp.126.7.983.

[22] G. A. Salum *et al.*, “High risk cohort study for psychiatric disorders in childhood: rationale, design, methods and preliminary results,” *Int J Methods Psychiatr Res*, vol. 24, no. 1, pp. 58–73, Mar. 2015, doi: 10.1002/mpr.1459.

[23] Wechsler D., “WISC-III: Escala de Inteligência Wechsler para Crianças: Manual. São Paulo: Casa do Psicólogo.” 2002.

[24] A. Vandierendonck, E. Kemps, M. C. Fastame, and A. Szmalec, “Working memory components of the Corsi blocks task,” *Br J Psychol*, vol. 95, no. Pt 1, pp. 57–79, Feb. 2004, doi: 10.1348/000712604322779460.

[25] A. M. Hogan, F. Vargha-Khadem, F. J. Kirkham, and T. Baldeweg, “Maturation of action monitoring from adolescence to adulthood: an ERP study,” *Dev Sci*, vol. 8, no. 6, pp. 525–534, Nov. 2005, doi: 10.1111/j.1467-7687.2005.00444.x.

[26] P. Bitsakou, L. Psychogiou, M. Thompson, and E. J. S. Sonuga-Barke, “Inhibitory deficits in attention-deficit/hyperactivity disorder are independent of basic processing efficiency and IQ,” *J Neural Transm (Vienna)*, vol. 115, no. 2, pp. 261–268, 2008, doi: 10.1007/s00702-007-0828-z.

[27] W. J. Youden, “Index for rating diagnostic tests,” *Cancer*, vol. 3, no. 1, pp. 32–35, Jan. 1950, doi: 10.1002/1097-0142(1950)3:1<32::aid-cncr2820030106>3.0.co;2-3.

[28] I. A. S. Bordin, J. J. Mari, and M. F. Caeiro, “Validação da versão brasileira do. [Validation of the Brazilian version of the Child Behavior Checklist (CBCL).],” *Revista ABP-APAL*, vol. 17, no. 2, pp. 55–66, 1995.

[29] T. M. Achenbach and T. M. Ruffle, “The Child Behavior Checklist and related forms for assessing behavioral/emotional problems and competencies,” *Pediatr Rev*, vol. 21, no. 8, pp. 265–271, Aug. 2000, doi: 10.1542/pir.21-8-265.

[30] M. Y. Ivanova *et al.*, “Testing the 8-syndrome structure of the child behavior checklist in 30 societies,” *J Clin Child Adolesc Psychol*, vol. 36, no. 3, pp. 405–417, Sep. 2007, doi: 10.1080/15374410701444363.

[31] R. Goodman, T. Ford, H. Richards, R. Gatward, and H. Meltzer, “The Development and Well-Being Assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology,” *J Child Psychol Psychiatry*, vol. 41, no. 5, pp. 645–655, Jul. 2000.

[32] R. Goodman, T. Ford, H. Simmons, R. Gatward, and H. Meltzer, “Using the Strengths and Difficulties Questionnaire (SDQ) to screen for child psychiatric disorders in a community sample,” *Br J Psychiatry*, vol. 177, pp. 534–539, Dec. 2000, doi: 10.1192/bjp.177.6.534.

[33] A. Stringaris and R. Goodman, “The value of measuring impact alongside symptoms in children and adolescents: a longitudinal assessment in a community sample,” *J Abnorm Child Psychol*, vol. 41, no. 7, pp. 1109–1120, Oct. 2013, doi: 10.1007/s10802-013-9744-x.

[34] C. H. Giacomoni, M. de L. Athayde, C. Zanon, and L. M. Stein, “Teste do Desempenho Escolar: evidências de validade do subteste de escrita,” *Psico-USF*, vol. 20, no. 1, pp. 133–140, Apr. 2015, doi: 10.1590/1413-82712015200112.

[35] C. A. Ibrahim-Verbaas *et al.*, “GWAS for executive function and processing speed suggests involvement of the CADM2 gene,” *Mol. Psychiatry*, vol. 21, no. 2, pp. 189–197, Feb. 2016, doi: 10.1038/mp.2015.37.

[36] D. Demontis *et al.*, “Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder,” *Nat Genet*, vol. 51, no. 1, pp. 63–75, Jan. 2019, doi: 10.1038/s41588-018-0269-7.

[37] J. J. Lee *et al.*, “Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals,” *Nat Genet*, vol. 50, no. 8, pp. 1112–1121, Aug. 2018, doi: 10.1038/s41588-018-0147-3.

[38] N. R. Wray *et al.*, “Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression,” *Nat Genet*, vol. 50, no. 5, pp. 668–681, May 2018, doi: 10.1038/s41588-018-0090-3.

[39] T. B. Bigdeli *et al.*, “Contributions of common genetic variants to risk of schizophrenia among individuals of African and Latino ancestry,” *Molecular Psychiatry*, pp. 1–13, Oct. 2019, doi: 10.1038/s41380-019-0517-y.

[40] Cross-Disorder Group of the Psychiatric Genomics Consortium, “Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide

analysis," *Lancet*, vol. 381, no. 9875, pp. 1371–1379, Apr. 2013, doi: 10.1016/S0140-6736(12)62129-1.

[41] J. Euesden, C. M. Lewis, and P. F. O'Reilly, "PRSice: Polygenic Risk Score software," *Bioinformatics*, vol. 31, no. 9, pp. 1466–1468, May 2015, doi: 10.1093/bioinformatics/btu848.

[42] B. Fischl, "FreeSurfer," *Neuroimage*, vol. 62, no. 2, pp. 774–781, Aug. 2012, doi: 10.1016/j.neuroimage.2012.01.021.

[43] Associação Brasiliera de Empresas de Pesquisa and Associação Brasiliera de Empresas de Pesquisa (ABEP), "Critério de Classificação Econômica Brasil," 2010.

[44] I. R. White, P. Royston, and A. M. Wood, "Multiple imputation using chained equations: Issues and guidance for practice," *Statistics in Medicine*, vol. 30, no. 4, pp. 377–399, 2011, doi: 10.1002/sim.4067.

[45] R Core Team, "R: A Language and Environment for Statistical Computing - R Foundation for Statistical Computing - avaliable at https://www.R-project.org/," 2019.

[46] D. A. Linzer and J. B. Lewis, "poLCA: An R Package for Polytomous Variable Latent Class Analysis," *Journal of Statistical Software*, vol. 42, no. 1, pp. 1–29, Jun. 2011, doi: 10.18637/jss.v042.i10.

[47] X. Robin *et al.*, "pROC: an open-source package for R and S+ to analyze and compare ROC curves," *BMC Bioinformatics*, vol. 12, no. 1, p. 77, Mar. 2011, doi: 10.1186/1471-2105-12-77.

[48] S. Wood and F. Scheipl, "Generalized Additive Mixed Models using 'mgcv' and 'lme4,'" 2017.

[49] S. van Buuren and K. Groothuis-Oudshoorn, "mice: Multivariate Imputation by Chained Equations in R," *Journal of Statistical Software*, vol. 45, no. 1, pp. 1–67, Dec. 2011, doi: 10.18637/jss.v045.i03.

[50] E. Feczko, O. Miranda-Dominguez, M. Marr, A. M. Graham, J. T. Nigg, and D. A. Fair, "The Heterogeneity Problem: Approaches to Identify Psychiatric Subtypes," *Trends Cogn. Sci. (Regul. Ed.)*, vol. 23, no. 7, pp. 584–601, Jul. 2019, doi: 10.1016/j.tics.2019.03.009.

[51] A. F. Marquand, T. Wolfers, M. Mennes, J. Buitelaar, and C. F. Beckmann, "Beyond Lumping and Splitting: A Review of Computational Approaches for Stratifying

Psychiatric Disorders," *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, vol. 1, no. 5, pp. 433–447, Sep. 2016, doi: 10.1016/j.bpsc.2016.04.002.

[52] J. Arnedo *et al.*, "Uncovering the hidden risk architecture of the schizophrenias: confirmation in three independent genome-wide association studies," *Am J Psychiatry*, vol. 172, no. 2, pp. 139–153, Feb. 2015, doi: 10.1176/appi.ajp.2014.14040435.

[53] B. A. Clementz *et al.*, "Identification of Distinct Psychosis Biotypes Using Brain-Based Biomarkers," *Am J Psychiatry*, vol. 173, no. 4, pp. 373–384, Apr. 2016, doi: 10.1176/appi.ajp.2015.14091200.

[54] A. T. Drysdale *et al.*, "Resting-state connectivity biomarkers define neurophysiological subtypes of depression," *Nat. Med.*, vol. 23, no. 1, pp. 28–38, 2017, doi: 10.1038/nm.4246.

[55] D. A. Fair, D. Bathula, M. A. Nikolas, and J. T. Nigg, "Distinct neuropsychological subgroups in typically developing youth inform heterogeneity in children with ADHD," *Proc. Natl. Acad. Sci. U.S.A.*, vol. 109, no. 17, pp. 6769–6774, Apr. 2012, doi: 10.1073/pnas.1115365109.

[56] A. Ing *et al.*, "Identification of neurobehavioural symptom groups based on shared brain mechanisms," *Nat Hum Behav*, Oct. 2019, doi: 10.1038/s41562-019-0738-8.

[57] C. J. Vaidya, X. You, S. Mostofsky, F. Pereira, M. M. Berl, and L. Kenworthy, "Data-driven identification of subtypes of executive function across typical development, attention deficit hyperactivity disorder, and autism spectrum disorders," *J Child Psychol Psychiatry*, Sep. 2019, doi: 10.1111/jcpp.13114.

[58] A. Kushki *et al.*, "Examining overlap and homogeneity in ASD, ADHD, and OCD: a data-driven, diagnosis-agnostic approach," *Transl Psychiatry*, vol. 9, no. 1, p. 318, 26 2019, doi: 10.1038/s41398-019-0631-2.

[59] J. Bathelt, J. Holmes, D. E. Astle, and Centre for Attention Learning and Memory (CALM) Team, "Data-Driven Subtyping of Executive Function-Related Behavioral Problems in Children," *J Am Acad Child Adolesc Psychiatry*, vol. 57, no. 4, pp. 252-262.e4, 2018, doi: 10.1016/j.jaac.2018.01.014.

[60] M. A. Nowrangi, C. Lyketsos, V. Rao, and C. A. Munro, "Systematic review of neuroimaging correlates of executive functioning: converging evidence from

different clinical populations," *J Neuropsychiatry Clin Neurosci*, vol. 26, no. 2, pp. 114–125, Apr. 2014, doi: 10.1176/appi.neuropsych.12070176.

[61] R. Siugzdaite, J. Bathelt, J. Holmes, and D. E. Astle, "Transdiagnostic Brain Mapping in Developmental Disorders," *Curr. Biol.*, vol. 30, no. 7, pp. 1245-1257.e4, Apr. 2020, doi: 10.1016/j.cub.2020.01.078.

[62] K. D. Bree and P. Beljan, "Neuro-Cognitive Intervention for Working Memory: Preliminary Results and Future Directions," *Appl Neuropsychol Child*, vol. 5, no. 3, pp. 202–213, Sep. 2016, doi: 10.1080/21622965.2016.1167504.

[63] A. Diamond and K. Lee, "Interventions Shown to Aid Executive Function Development in Children 4 to 12 Years Old," *Science*, vol. 333, no. 6045, pp. 959–964, Aug. 2011, doi: 10.1126/science.1204529.

[64] T. M. Otero, L. A. Barker, and J. A. Naglieri, "Executive function treatment and intervention in schools," *Appl Neuropsychol Child*, vol. 3, no. 3, pp. 205–214, 2014, doi: 10.1080/21622965.2014.897903.

[65] C. A. Riccio and H. Gomes, "Interventions for executive function deficits in children and adolescents," *Appl Neuropsychol Child*, vol. 2, no. 2, pp. 133–140, 2013, doi: 10.1080/21622965.2013.748383.

[66] E. Blakey and D. J. Carroll, "A Short Executive Function Training Program Improves Preschoolers' Working Memory," *Front Psychol*, vol. 6, p. 1827, 2015, doi: 10.3389/fpsyg.2015.01827.

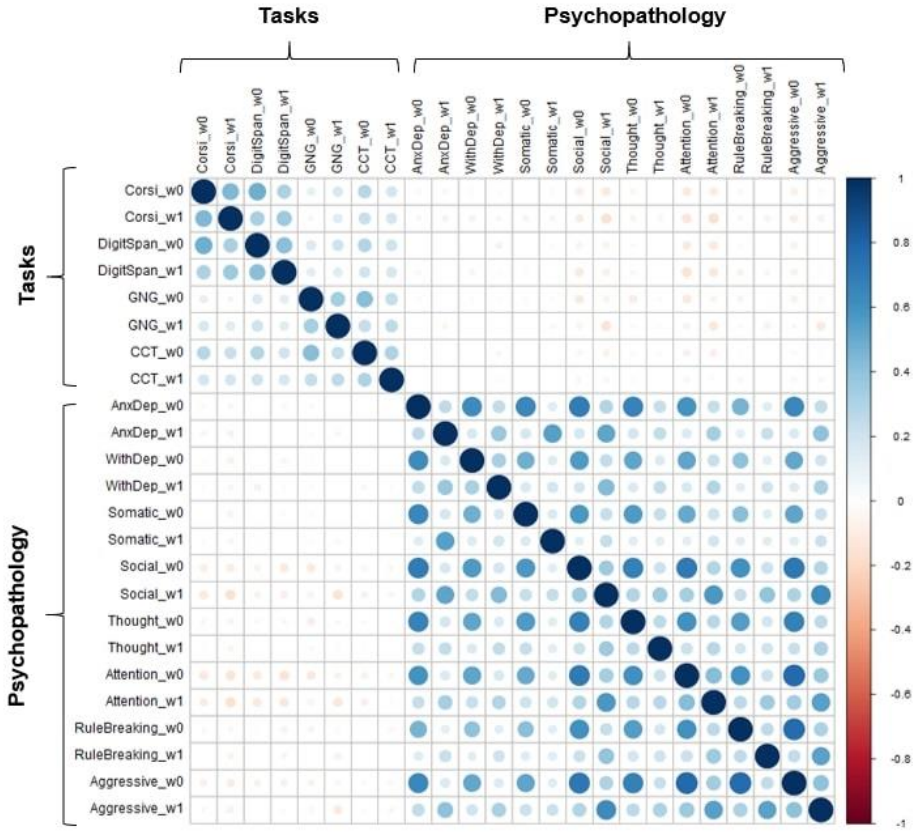
[67] S. M. Dowsett and D. J. Livesey, "The development of inhibitory control in preschool children: Effects of 'executive skills' training," *Developmental Psychobiology*, vol. 36, no. 2, pp. 161–174, 2000, doi: 10.1002/(SICI)1098-2302(200003)36:2<161::AID-DEV7>3.0.CO;2-0.

[68] A. Pandey, D. Hale, S. Das, A.-L. Goddings, S.-J. Blakemore, and R. M. Viner, "Effectiveness of Universal Self-regulation-Based Interventions in Children and Adolescents: A Systematic Review and Meta-analysis," *JAMA Pediatr*, vol. 172, no. 6, pp. 566–575, 01 2018, doi: 10.1001/jamapediatrics.2018.0232.

[69] D. A. Robson, M. S. Allen, and S. J. Howard, "Self-regulation in childhood as a predictor of future outcomes: A meta-analytic review," *Psychol Bull*, Jan. 2020, doi: 10.1037/bul0000227.

FIGURES

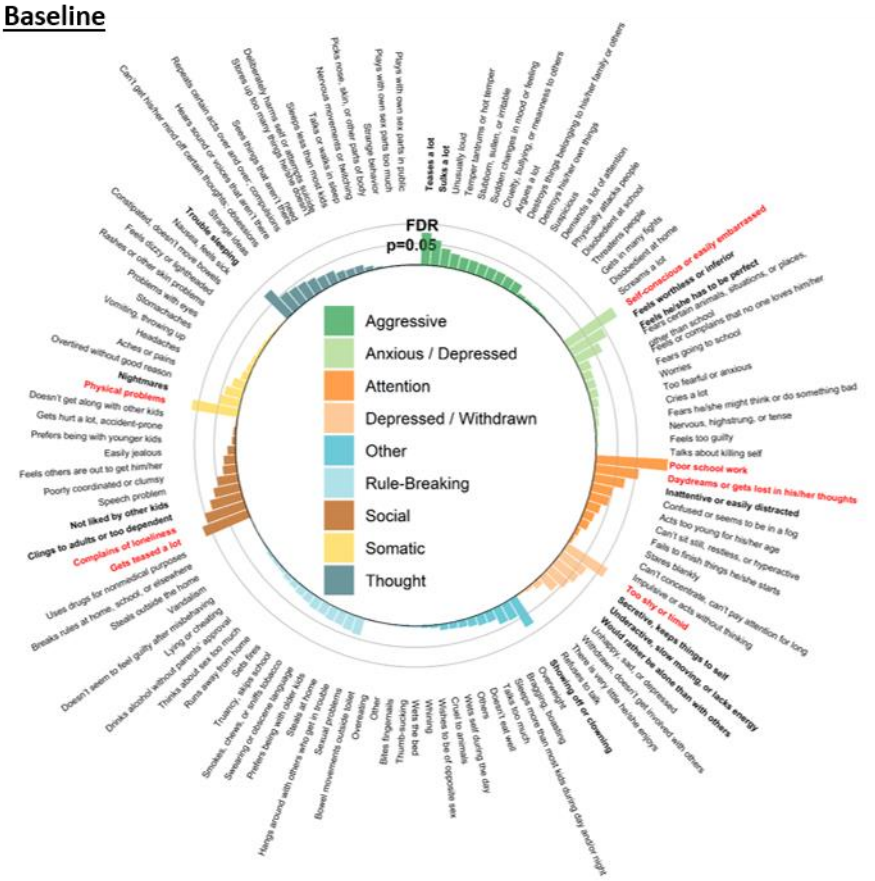
Figure 1- Correlation plot of executive function tasks and domains of psychopathology at baseline and follow-up



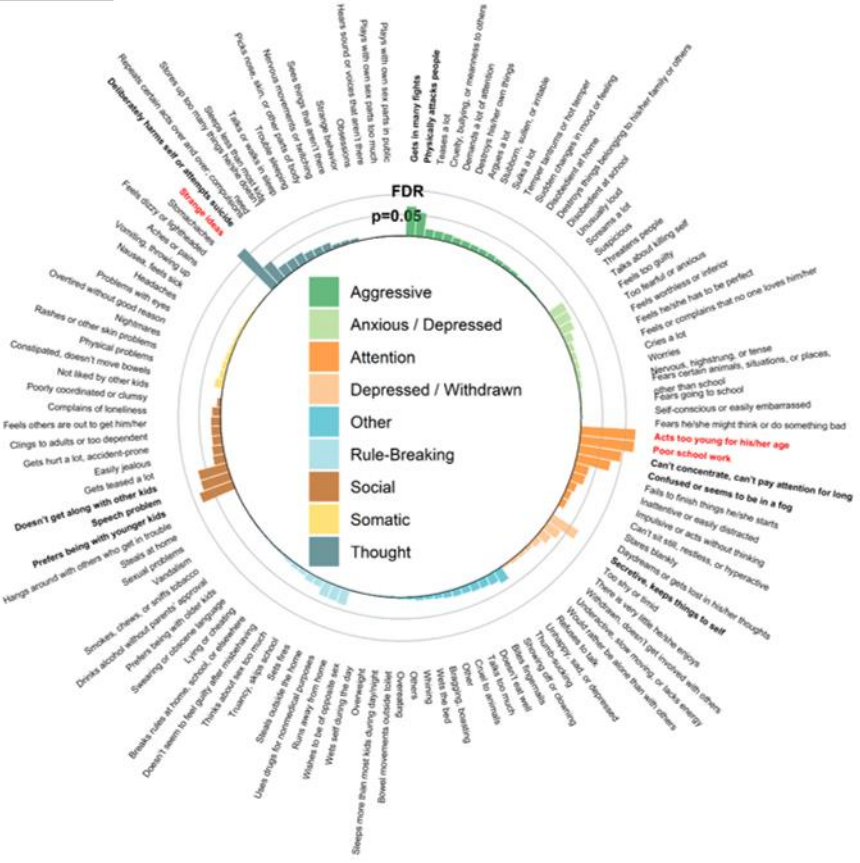
Abbreviations: AnxDep – Anxious/Depressed; WithDep – Withdrawn/Depressed; W0 – Baseline Assessment; W1 – Follow-Up Assessment

Figure 2 - Bottom-up symptomatology of the EDC

Baseline

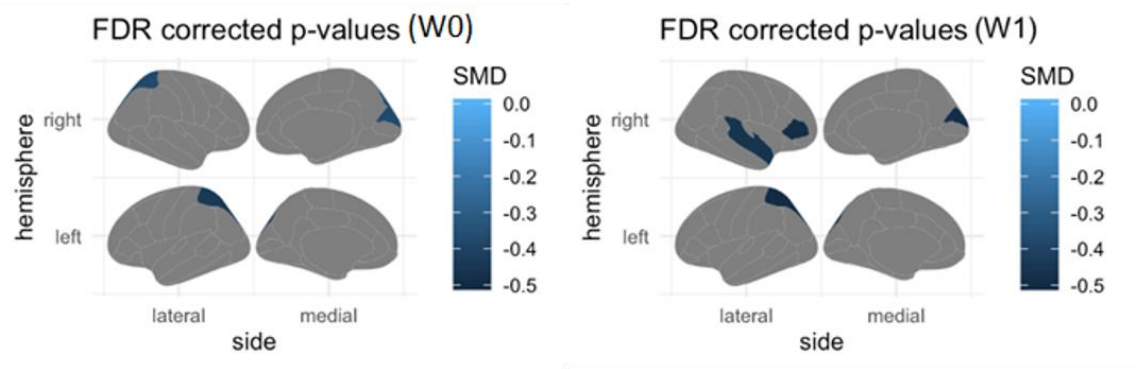


Follow-Up



Observations: graphs show the -log(p) for multiple logistical regressions. The reference lines mark p=0.05 and the False Discovery Rate (FDR) threshold. Variables below the 0.05 threshold are signaled in bold and those over FDR threshold are marked in red.

Figure 3 – Cortical Surface Areas Associated with Executive Dysfunction Class in baseline and follow-up assessments



Abbreviations: W0 – Baseline Assessment; W1 – Follow-Up Assessment; SMD – Standardized Mean Difference

Table 1: Assessment of Functional Impairment – School/Education, Family Life and Friendships									
	Cross-Sectional Baseline Associations			**Cross-Sectional Follow-Up Associations**			**Longitudinal Predictions**		
School Impairment	**OR**	***CI 95%***	***p***	**OR**	***CI 95%***	***p***	**OR**	***CI 95%***	***p***
SDQ school impairment	1.751	1.303; 2.354	<0.001*	1.248	0.786; 1.983	0.347	1.212	0.849; 1.731	0.290
SDQ school impairment (Teacher-Rated)[1]	1.618	1.012; 2.588	0.044*	-	-	-	-	-	-
Any Adverse School Event	2.530	1.838; 3.483	<0.001*	1.624	1.093; 2.414	0.016*	1.373	0.997; 1.891	0.052
	SMD	***CI 95%***	***p***	**SMD**	***CI 95%***	***p***	**SMD**	***CI 95%***	***p***
Non-Attendence[2]	0.178	0.129; 0.227	<0.001*	0.097	0.011; 0.183	0.026*	0.071	0.003; 0.140	0.041*
Achievement[2]	-0.245	-0.353; -0.137	<0.001*	-0.196	-0.358; -0.034	0.017*	-0.244	-0.367; -0.121	<0.001*
Literacy[2]	-0.410	-0.499; -0.321	<0.001*	-0.395	-0.525; -0.265	<0.001*	-0.064	-0.158; 0.023	0.147
Family Life Impairment	**OR**	***CI 95%***	***p***	**OR**	***CI 95%***	***p***	**OR**	***CI 95%***	***p***
SDQ family life impairment	1.571	1.083; 2.280	0.017*	0.827	0.439; 1.559	0.557	0.939	0.599; 1.473	0.784
SDQ family life impairment (Teacher-Rated)[1]	1.534	0.973; 2.417	0.065	-	-	-	-	-	-
Friendship Impairment	**OR**	***CI 95%***	***p***	**OR**	***CI 95%***	***p***	**OR**	***CI 95%***	***p***
SDQ friendship impairment	1.281	0.861; 1.904	0.220	1.301	0.662; 2.557	0.445	1.176	0.701; 1.971	0.539
SDQ friendship impairment (Teacher-Rated)[1]	1.715	1.179; 2.493	0.004*	-	-	-	-	-	-

Observations:
[1] Data only available for a subsample of the baseline assessment;
[2] Mean standardized factor score
Abbreviations: SMD – Standardized Mean Difference; OR – Odds Ratio; CI – Confidence Interval.
* p-values bellow 0.05.

Table 2: Assessment of Biological Validators - Neuroimage & Polygenic Risk Scores						
	Cross-Sectional Baseline Associations			Cross-Sectional Follow-Up Associations		
	SMD	***t***	***p***	***SMD***	***t***	***p***
Neuroimage						
Intracranial Volume	-0.206	-1.898	0.058	-0.309	-2.008	0.045*
Left Cortical Thickness	0.169	1.445	0.149	0.183	1.203	0.230
Right Cortical Thickness	0.201	1.711	0.087	0.116	0.75	0.454
Left Surface Area	-0.280	-2.518	0.012*	-0.436	-2.997	0.003*
Right Surface Area	-0.259	-2.347	0.019*	-0.447	-3.11	0.002*
Polygenic Risk Scores						
ADHD	0.153	2.534	0.011*	0.014	0.159	0.874
MDD	0.046	0.921	0.357	-0.046	-0.640	0.522
SCZ	0.008	0.303	0.761	0.102	2.736	0.006*
Education Attainment	-0.145	-2.328	0.020*	-0.145	-1.592	0.111
Cross-Disorder	-0.094	-1.761	0.078	0.001	0.018	0.986

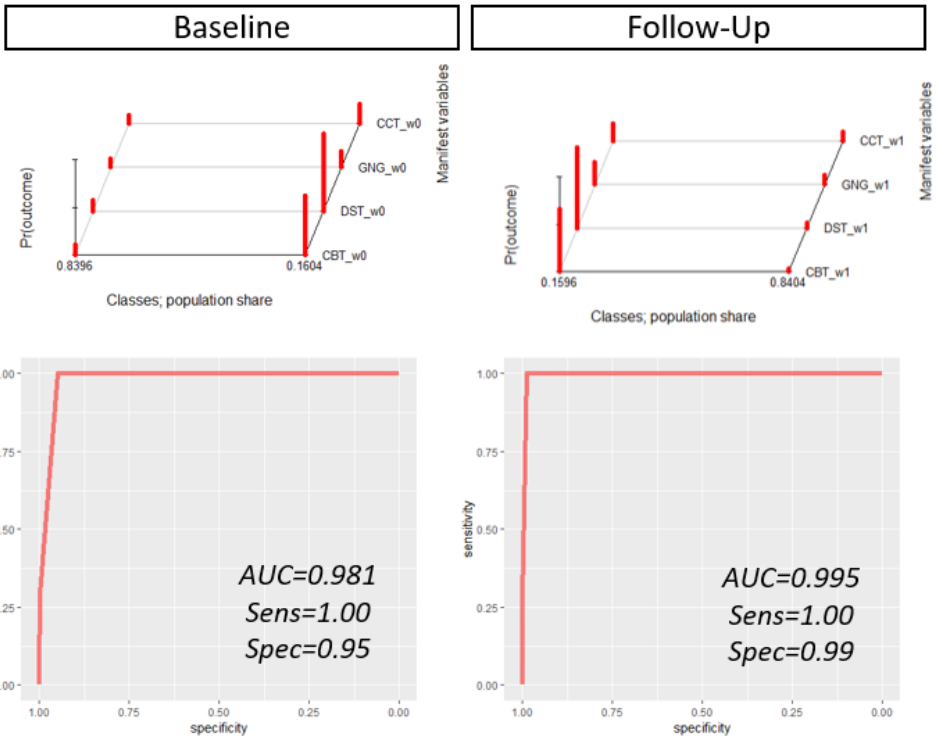
Observations:
[1] Mean standardized factor score (as depicted in Methods);
[2] Data only available for baseline.
Abbreviations: SMD – Standardized Mean Difference; ADHD – Attention Deficit/Hyperactivity Disorder; SCZ – Schizophrenia; MDD – Major Depression Disorder.
* p-values bellow 0.05

SUPPLEMENTAL MATERIAL

Table S1: Test Results Thresholds							
		Males			*Females*		
		Baseline					
	Age	***N subjects***	***Mean***	***p.10***	***N subjects***	***Mean***	***p.10***
Corsi Blocks Test	6-7	76	3.64	1.5	64	3.31	2
	8-9	152	4.49	2	142	4.49	2
	10-11	144	5.37	3	121	5.48	3
	12-13	75	6.03	4	76	5.70	3
Digit Span Task	6-7	79	2.53	0	65	2.55	1
	8-9	154	3.36	2	144	3.37	2
	10-11	144	3.81	2	122	4.02	2
	12-13	76	4.28	3	77	4.29	3
Go/No-Go Task[1]	6-7	78	0.364	0.753	63	0.297	0.617
	8-9	154	0.261	0.625	138	0.227	0.52
	10-11	133	0.279	0.620	122	0.195	0.498
	12-13	73	0.248	0.620	76	0.137	0.32
Conflict Control Task	6-7	81	0.468	0.2	61	0.508	0.208
	8-9	156	0.571	0.24	140	0.581	0.276
	10-11	134	0.607	0.32	124	0.662	0.412
	12-13	73	0.648	0.336	74	0.722	0.542
		Follow-up					
Corsi Blocks Test	9-10	52	4.77	2	37	4.73	1.6
	11-12	120	5.22	2	120	5.39	2
	13-14	147	6.45	4	97	5.75	2.6
	15-17	74	6.03	2	72	5.18	0
Digit Span Task	9-10	52	3.40	2	37	4.08	2
	11-12	120	3.87	2	120	4.21	2
	13-14	147	4.61	3	97	4.40	2
	15-17	74	4.42	2	72	4.19	0
Go/No-Go Task[1]	9-10	49	0.298	0.728	35	0.228	0.547
	11-12	108	0.228	0.583	114	0.159	0.393
	13-14	134	0.167	0.433	88	0.146	0.372
	15-17	67	0.141	0.339	61	0.102	0.25
Conflict Control Task	9-10	49	0.456	0	35	0.615	0.326
	11-12	107	0.621	0.246	114	0.619	0.036
	13-14	134	0.678	0.0905	88	0.729	0.494
	15-17	68	0.725	0.52	62	0.680	0.0333

Observations:
[1] In the Go/No-Go, the lower the result, the better; So, p90 was used as the threshold.

Panel S1- Operationalization of EDC



Operationalization Summary and Fit				
	Baseline		Follow-Up	
	Cases	*Controls*	*Cases*	*Controls*
FIT LCA	AIC(2): 7019.345 BIC(2): 7070.639 G^2(2): 35.91064 X^2(2): 48.36151		AIC(2): 4756.089 BIC(2): 4807.384 G^2(2): 67.97451 X^2(2): 52.06312	
% LCA	0.11	0.89	0.10	0.90
% EDC	0.16	0.84	0.09	0.91
Observations: LCA – Latent Class Analysis; EDC – Executive Dysfunction Class				

Figure S1 - Operationalization of the Executive Dysfunction Class

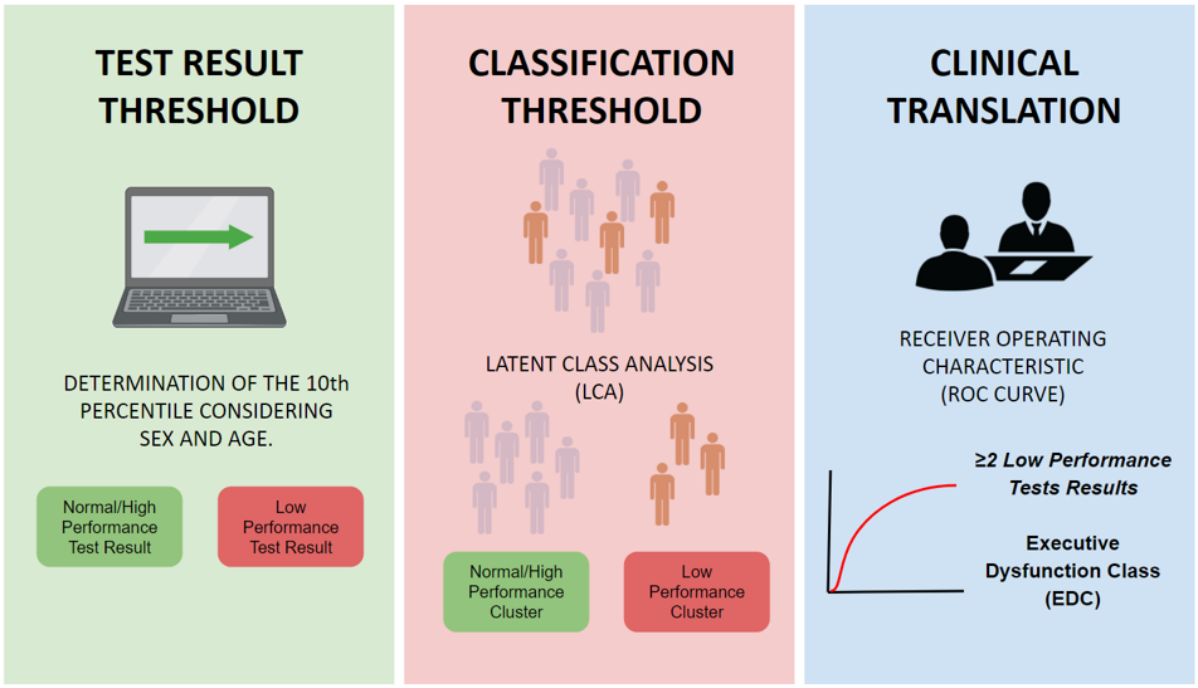


Table S2: Sample Description – Demographics & Mental Disorders								
	Baseline				Follow-Up			
	Controls	EDC			Controls	EDC		
	Mean		t	p	Mean		t	p
Demographics								
Age	10.18	10.25	-0.525	0.6	13.44	13.14	1.820	0.07
SES[1]	21.80	20.45	4.812	<0.001*	21.72	20.63	2.929	0.004*
	n/total (%)		OR (CI 95%)		n/total (%)		OR (CI 95%)	
Demographics								
Sex (males)	908/1623 (55.9%)	147/307 (47.9%)	0.72* (0.57-0.92)		766/1396 (54.9%)	89/135 (65.9%)	1.59* (1.10-2.31)	
Psychiatric Disorders								
Any	420/1623 (25.9%)	95/307 (30.9%)	1.28 (0.98-1.68)		328/1396 (23.5%)	35/135 (25.9%)	1.14 (0.76-1.71)	
ADHD	171/1623 (10.5%)	39/307 (12.7%)	1.24 (0.85-1.79)		70/1396 (5.0%)	8/135 (5.9%)	1.19 (0.56-2.54)	
Conduct	103/1623 (6.3%)	27/307 (8.8%)	1.42 (0.91-2.22)		72/1396 (5.1%)	8/135 (5.9%)	1.16 (0.55-2.46)	
Anxiety	86/1623 (5.3%)	16/307 (8.8%)	0.98 (0.57-1.70)		133/1396 (9.5%)	15/135 (11.1%)	1.19 (0.67-2.09)	
Depression	48/1623 (3.0%)	12/307 (3.9%)	1.33 (0.70-2.54)		102/1396 (7.3%)	9/135 (6.7%)	0.91 (0.45-1.84)	

Observations:
[1] Ranges from 3-40, the higher the better the socioeconomic score.
* p-values below 0.05

Table S3: High-Order Psychiatric Diagnoses						
	Cross-Sectional Baseline Associations			Cross-Sectional Follow-Up Associations		
	OR	*CI 95%*	*p*	OR	*CI 95%*	*p*
ADHD	1.038	0.687-1.563	0.863	0.830	0.345-1.197	0.677
Conduct Disorders	1.243	0.757-2.041	0.390	1.079	0.465-2.505	0.858
Anxiety Disorders	0.849	0.478-1.507	0.575	1.030	0.565-1.878	0.923
Depression Disorders	1.091	0.550-2.166	0.803	1.123	0.518-2.436	0.769

Observations:
Abbreviations: OR – Odds Ratio; ADHD – Attention Deficit/Hyperactivity Disorder.

Table S4: Assessment of Longitudinal Functional Impairment – Supplemental Analysis Using Multiple Imputation by Chained Equations			
	Longitudinal Predictions		
School Impairment	**OR**	***CI 95%***	***p***
SDQ school impairment	1.212	0.849; 1.731	0.290
Any Adverse School Event	1.373	0.997; 1.891	0.052
	SMD	***CI 95%***	***p***
Non-Attendence[1]	0.071	0.003; 0.140	0.041*
Achievement[1]	-0.244	-0.367; -0.121	<0.001*
Literacy[1]	-0.064	-0.158; 0.023	0.147
Family Life Impairment	**OR**	***CI 95%***	***p***
SDQ family life impairment	0.939	0.599; 1.473	0.784
Friendship Impairment	**OR**	***CI 95%***	***p***
SDQ friendship impairment	1.176	0.701; 1.971	0.539

Observations:
[1] Mean standardized factor score
Abbreviations: SMD – Standardized Mean Difference; OR – Odds Ratio; CI – Confidence Interval.
* p-values bellow 0.05-

Table S5: Cortical Surface Areas								
	Cross-Sectional Baseline Associations				Cross-Sectional Follow-Up Associations			
	SMD	*t*	*p*	*p adj*	*SMD*	*t*	*p*	*p adj*
LEFT								
Banks Superior Temporal	-0.087	-0.695	0.487	0.614	0.091	0.546	0.585	0.622
Caudal Anterior Cingulate	-0.074	-0.577	0.564	0.685	-0.116	-0.680	0.497	0.563
Caudal Middle Frontal	-0.237	-1.917	0.056	0.219	-0.143	-0.846	0.398	0.484
Cuneus	-0.348	-2.880	0.004	0.070	-0.294	-1.955	0.051	0.106
Entorhinal	-0.141	-1.111	0.267	0.420	-0.124	-0.733	0.464	0.544
Fusiform	-0.238	-1.996	0.046	0.197	-0.394	-2.642	0.009	0.074
Inferior Parietal	-0.112	-0.890	0.374	0.498	-0.350	-2.343	0.020	0.078
Inferior Temporal	-0.139	-1.138	0.256	0.414	-0.251	-1.618	0.107	0.181
Isthmus Cingulate	-0.027	-0.211	0.833	0.914	-0.127	-0.817	0.415	0.495
Lateral Occipital	-0.117	-1.039	0.299	0.420	-0.319	-2.269	0.024	0.081
Lateral Orbitofrontal	-0.215	-1.831	0.068	0.219	-0.235	-1.576	0.116	0.184
Lingual	-0.196	-1.617	0.107	0.239	-0.243	-1.552	0.122	0.188
Medial Orbito Frontal	-0.212	-1.882	0.060	0.219	-0.285	-1.876	0.061	0.123
Middle Temporal	-0.153	-1.270	0.205	0.366	-0.279	-1.805	0.072	0.136
Parahippocampal	-0.150	-1.160	0.247	0.409	0.000	-0.001	0.999	0.999
Para Central	-0.284	-2.307	0.021	0.104	-0.351	-2.137	0.033	0.090
Pars Opercularis	-0.162	-1.255	0.210	0.366	-0.345	-2.109	0.036	0.090
Pars Orbitalis	-0.315	-2.611	0.009	0.083	-0.218	-1.438	0.151	0.229
Pars Triangularis	-0.194	-1.537	0.125	0.257	-0.357	-2.209	0.028	0.086
Pericalcarine	-0.202	-1.673	0.095	0.239	-0.355	-2.339	0.020	0.078
Post Central	-0.202	-1.688	0.092	0.239	-0.317	-2.038	0.042	0.096
Posterior Cingulate	-0.018	-0.148	0.882	0.924	-0.094	-0.567	0.571	0.622
Pre central	-0.123	-1.033	0.302	0.420	-0.391	-2.480	0.014	0.074
Precuneus	-0.319	-2.591	0.010	0.083	-0.319	-2.115	0.035	0.090
Rostral Anterior Cingulate	-0.170	-1.391	0.165	0.326	-0.153	-0.888	0.375	0.464
Rostral Middle Frontal	-0.306	-2.683	0.008	0.083	-0.386	-2.560	0.011	0.074
Superior Frontal	-0.162	-1.379	0.169	0.326	-0.326	-1.974	0.049	0.104
Superior Parietal	-0.439	-3.508	0.000	0.033*	-0.492	-3.171	0.002	0.032*
Superior Temporal	-0.191	-1.606	0.109	0.239	-0.277	-1.772	0.077	0.142
Supramarginal	-0.130	-1.058	0.290	0.420	-0.378	-2.393	0.017	0.078
Frontal Pole	-0.019	-0.153	0.878	0.924	0.005	0.031	0.975	0.989
Temporal Pole	-0.015	-0.120	0.905	0.924	-0.059	-0.356	0.722	0.756
Transverse Temporal	-0.060	-0.480	0.632	0.741	-0.276	-1.663	0.097	0.169
Insula	-0.098	-0.813	0.416	0.534	-0.313	-1.991	0.047	0.104
RIGHT								
Banks Superior Temporal	-0.215	-1.692	0.091	0.239	-0.504	-3.202	0.001	0.032*
Caudal Anterior Cingulate	-0.174	-1.366	0.173	0.326	-0.395	-2.311	0.021	0.078
Caudal Middle Frontal	-0.217	-1.784	0.075	0.222	-0.364	-2.156	0.032	0.090
Cuneus	-0.371	-3.141	0.002	0.047*	-0.477	-3.105	0.002	0.032*
Entorhinal	-0.205	-1.648	0.100	0.239	0.118	0.705	0.481	0.554
Fusiform	-0.300	-2.544	0.011	0.083	-0.399	-2.565	0.011	0.074
Inferior Parietal	-0.128	-1.032	0.303	0.420	-0.233	-1.590	0.113	0.184
Inferior Temporal	-0.050	-0.428	0.668	0.758	-0.358	-2.355	0.019	0.078
Isthmus Cingulate	-0.078	-0.616	0.538	0.665	-0.210	-1.404	0.161	0.238
Lateral Occipital	-0.292	-2.516	0.012	0.083	-0.169	-1.168	0.244	0.307
Lateral Orbitofrontal	-0.184	-1.623	0.105	0.239	-0.091	-0.621	0.535	0.597
Lingual	-0.288	-2.339	0.020	0.103	-0.204	-1.308	0.192	0.262

Medial Orbito Frontal	-0.143	-1.216	0.225	0.382	-0.179	-1.198	0.232	0.303
Middle Temporal	-0.052	-0.428	0.669	0.758	-0.395	-2.587	0.010	0.074
Parahippocampal	-0.107	-0.834	0.405	0.529	-0.035	-0.208	0.836	0.861
Para Central	-0.283	-2.230	0.026	0.119	-0.338	-2.088	0.038	0.091
Pars Opercularis	-0.199	-1.591	0.112	0.239	-0.359	-2.192	0.029	0.086
Pars Orbitalis	-0.152	-1.286	0.199	0.365	-0.237	-1.573	0.117	0.184
Pars Triangularis	-0.014	-0.113	0.910	0.924	-0.486	-3.064	0.002	0.032*
Pericalcarine	-0.279	-2.349	0.019	0.103	-0.360	-2.305	0.022	0.078
Post Central	-0.293	-2.445	0.015	0.091	-0.320	-2.042	0.042	0.096
Posterior Cingulate	-0.199	-1.620	0.106	0.239	-0.198	-1.223	0.222	0.296
Pre central	-0.315	-2.669	0.008	0.083	-0.388	-2.496	0.013	0.074
Precuneus	-0.228	-1.861	0.063	0.219	-0.281	-1.864	0.063	0.123
Rostral Anterior Cingulate	-0.226	-1.793	0.074	0.222	-0.198	-1.168	0.243	0.307
Rostral Middle Frontal	0.010	0.085	0.932	0.932	-0.340	-2.212	0.028	0.086
Superior Frontal	-0.129	-1.096	0.273	0.420	-0.395	-2.468	0.014	0.074
Superior Parietal	-0.375	-3.097	0.002	0.047*	-0.529	-3.325	0.001	0.032*
Superior Temporal	-0.133	-1.070	0.285	0.420	-0.462	-2.974	0.003	0.036*
Supramarginal	-0.224	-1.85	0.065	0.219	-0.221	-1.366	0.173	0.245
Frontal Pole	-0.016	-0.128	0.898	0.924	-0.198	-1.306	0.193	0.262
Temporal Pole	-0.067	-0.534	0.594	0.708	-0.093	-0.556	0.578	0.622
Transverse Temporal	-0.125	-0.983	0.326	0.443	-0.213	-1.368	0.172	0.245
Insula	-0.047	-0.389	0.697	0.777	-0.270	-1.697	0.091	0.162

Observations:
Adjustment for multiple comparisons made by False Discovery Rate (FDR).
Abbreviations: SMD – Standardized Mean Difference.
* p-values bellow 0.05

Table S6: Comparison Between EDC and Individual EF Tasks										
	EDC		**Corsi Blocks**		**Digit Span**		**Go/No-Go**		**Conflict Control**	
	OR	***CI 95%***	**OR**	***CI 95%***	**OR**	***CI 95%***	**OR**	***CI 95%***	**OR**	***CI 95%***
Stability										
Prediction of itself	5.017	3.415; 7.636	3.151	2.329; 4.264	3.017	2.318; 3.928	3.268	2.141; 4.989	1.657	1.024; 2.682
Family Life Impairment										
SDQ family life impairment	1.571	1.083; 2.280	1.533	1.098; 2.139	1.209	0.885; 1.650	1.219	0.786; 1.890	1.784	1.172; 2.714
SDQ family life impairment (Teacher-Rated)	1.534	0.973; 2.417	1.324	0.874; 2.005	1.515	1.029; 2.231	1.701	1.010; 2.863	1.412	0.822; 2.426
Friendship Impairment										
SDQ friendship impairment	1.281	0.861; 1.904	1.220	0.855; 1.740	1.331	0.962; 1.841	1.059	0.657; 1.707	1.358	0.857; 2.150
SDQ friendship impairment (Teacher-Rated)	1.715	1.179; 2.493	1.574	1.121; 2.212	1.728	1.253; 2.385	1.088	0.682; 1.737	1.646	1.058; 2.560
School Impairment										
SDQ school impairment	1.751	1.303; 2.354	1.196	0.913; 1.567	1.568	1.227; 2.002	1.443	1.026; 2.030	1.754	1.253; 2.457
SDQ school impairment (Teacher-Rated)	1.618	1.012; 2.588	1.555	1.008; 2.399	1.627	1.087; 2.440	1.128	0.617; 2.062	1.245	0.698; 2.219
Any Adverse School Event	2.530	1.838; 3.483	1.421	1.057; 1.908	2.146	1.648; 2.794	1.392	0.963; 2.011	1.733	1.209; 2.486
	SMD	***CI 95%***	**SMD**	***CI 95%***	**SMD**	***CI 95%***	**SMD**	***CI 95%***	**SMD**	***CI 95%***
Non-Attendence[1]	0.178	0.129; 0.227	0.064	0.015; 0.112	0.147	0.102; 0.192	0.061	-0.004; 0.126	0.074	0.011; 0.137
Achievement[1]	-0.245	-0.353; -0.137	-0.223	-0.333; -0.113	-0.234	-0.335; -0.133	-0.115	-0.261; 0.031	-0.148	-0.288; -0.008
Literacy[1]	-0.410	-0.499; -0.321	-0.286	-0.381; -0.191	-0.392	-0.479; -0.305	-0.103	-0.226; 0.020	-0.180	-0.297; -0.062
Polygenic Risk Scores										
ADHD	0.153	0.035; 0.272	0.151	0.035; 0.268	0.037	-0.069; 0.144	0.077	-0.079; 0.234	0.039	-0.108; 0.186
MDD	0.046	-0.052; 0.145	-0.013	-0.112; 0.087	-0.024	-0.115; 0.068	0.113	-0.018; 0.244	-0.020	-0.104; 0.144
SCZ	0.008	-0.043; 0.059	0.021	-0.029; 0.071	0.013	-0.033; 0.059	0.036	-0.031; 0.103	0.024	-0.038; 0.087
Education Attainment	-0.145	-0.268; -0.023	-0.110	-0.232; 0.013	-0.115	-0.227; -0.003	0.101	-0.061; 0.234	-0.101	-0.254; 0.051
Cross-Disorder	-0.094	-0.199; 0.011	0.029	-0.075; 0.133	-0.073	-0.167; 0.023	0.017	-0.121; 0.155	-0.010	-0.140; 0.121

Observations:
[1] Mean standardized factor score
Abbreviations: SMD – Standardized Mean Difference; OR – Odds Ratio; CI – Confidence Interval.

5. CONCLUSÕES E CONSIDERAÇÕES FINAIS

Nesta tese foram apresentados dois artigos que objetivaram avaliar aspectos referentes aos métodos de classificação dos transtornos mentais, seja testando empiricamente os métodos vigentes, seja propondo novas metodologias de classificação.

O primeiro estudo avaliou a existência de casos de TDAH de início na adolescência. O estudo abordou falhas da literatura prévia, excluindo casos subsindrômicos de TDAH, e investigou especificamente o período da adolescência como faixa de incidência o TDAH. Ademais, o estudo analisou mais extensamente características pré-mórbidas dos indivíduos acometidos pelo TDAH de início na adolescência. Conclue-se que os jovens com TDAH de início tardio, apesar de não apresentarem outros diagnósticos psiquiátrico na infância, já apresentavam maior psicopatologia dimensional, maior fator P[3] e pior desfecho cognitivo. Dessa forma, não negando a existência de casos de início tardio, o estudo hipotetiza que tais participantes provavelmente apresentam um curso heterotípico de psicopatologia, que pode se manifestar mais tardiamente como sintomas de hiperatividade e desatenção.

Uma revisão de todos os estudos acerca do TDAH de início tardio foi publicada em 2019 por Philip Asherson, que conclui que casos de TDAH com significativo prejuízo podem incidir após os 12 anos de idade, embora raramente sem um contexto prévio de precursores psicopatológicos. De tal forma, após uma avaliação completa sobre outros transtornos mentais comórbidos, os clínicos não deveriam se abster de diagnosticar e tratar indivíduos com TDAH de início fora do estipulado pelos manuais diagnósticos [51].

[3] Conceitualiza-se o “fator P” como a variância compartilhada entre os transtornos mentais, investigada por meio de modelos bifatoriais, capazes de distinguir fatores específicos e comuns relacionados à psicopatologia [49], [50].

Tal conclusão está baseada nas fortes evidências vistas para indivíduos com trajetórias normativas de TDAH que a ausência de tratamento está relacionada à diversas condições adversas. Dessa forma, negar tratamento a indivíduos acometidos pelo fenótipo de desatenção e hiperatividade simplesmente pelo fato de eles não cumprirem um critério que é primariamente arbitrário não deveria ser considerada boa prática. O tópico de TDAH de início tardio, no entanto, segue sendo foco de investigações.

O segundo estudo testou um método de classificação baseado exclusivamente em critérios objetivos de medição das funções executivas de crianças e adolescentes. Baseado na ideia do RDoC de avaliar mecanismos classificatórios objetivos, com uma abordagem “de baixo para cima”, o estudo operacionalizou um critério clinicamente plausível para distinguir uma classe de participantescom déficits em funções executivas e avaliou a estabilidade e a validade desse novo constructo. Evidenciou-se que a classe de disfunção executiva era razoavelmente estável ao longo do tempo e associava-se com diversos validadores, mesmo após correção para fatores socioeconômicos, inteligência e diagnósticos psiquiátricos. Tais associações foram observadas com sintomas, prejuízo em diferentes ambientes, aspectos genéticos e de neuroimagem estrutural. Dessa forma, concluiu-se que a classificação construída apenas por testes aumentava a objetividade da avaliação classificatória e era capaz de identificar indivíduos com prejuízo funcional, além de relacionar-se com correlatos biológicos. Nesse contexto, abre-se possibilidade para que invervenções mais precoces e específicas possam ser aplicadas em crianças com déficits identificados pelo método.

Ao testar a operacionalização de um critério classificatório objetivo e mostrar sua funcionalidade prática, o estudo foi capaz de demonstrar que o desenvolvimento de classes objetivas, sejam elas relacionadas às funções excutivas, sejam elas baseadas em

outros constructos, pode futuramente tornar-se um método de avaliação clínica. Tais achados reforçam a ideia de que métodos de classificação heterodoxos devem ser avalidos pela pesquisa psiquiátrica, porém ressalta que a capacidade de validação externa e utilização prática desses métodos depende de sua operacionalização. Tal conclusão lança um novo desafio para estratégias como o RDoC, que apesar de uma crescente força no meio acadêmico, ainda não foi capaz de demonstrar plenamente uma funcionalidade clínica direta.

Os estudos que compuseram essa teste tem o objetivo de mostrar a importância da testagem empírica dos processos classificatórios em psiquiatria. Tal testagem é capaz de avaliar erros da metodologia descritiva-fenomenológica, assim como apontar capacidades potenciais e dificuldades futuras para sistemas que visam maior objetividade biológica. Apesar de reconhecer as falhas dos sistemas classificatórios atuais, ainda carecem evidências de que os métodos alternativos sejam superiores ao modelo vigente, apesar de seu apelo teórico. O segundo estudo da tese demonstrou que tal abordagem é capaz de identificar problemas de funcionamento de jovens que, apesar de não terem alta prevalência de transtornos mentais, apresentam déficits de funções executivas objetivamente medidos. Concluiu-se que a capacidade de identificar prejuízo era possível usando tais critérios objetivos, porém não se pode afirmar que ela seja superior. Da mesma forma, a associação com validadores biológicos não é por si só capaz de demonstrar superioridade, de forma que a cautela e a avaliação criteriosa devem embasar os estudos futuros refentes à nosologia psiquiátrica e a incorporação de métodos alternativos de classificação. As próximas versões dos manuais baseados na fenomenologia cada vez mais enfrentarão o dilema entre manter um modelo epistêmico

reconhecendo suas fragilidades ou adotar um modelo alternativo, cujas fragilidades clínicas estão longe de serem conhecidas [52].

A incorporação dos conhecimentos adquiridos com as neurociências com o atual modelo descritivo de psicopatologia provavelmente manterá seu papel e ganhará força no futuro próximo. O papel da pesquisa irá se tornar cada vez mais essencial em avaliar as limitações dos modelos classificatórios e empiricamente testar suas qualidades e capacidades.

6. REFERÊNCIAS

[1] American Psychiatric Association, Diagnostic and statistical manual of mental disorders - 3th edition. 1980.

[2] K. S. Kendler, “An historical framework for psychiatric nosology,” Psychol Med, vol. 39, no. 12, pp. 1935–1941, Dec. 2009, doi: 10.1017/S0033291709005753.

[3] K. S. Kendler, “The nature of psychiatric disorders,” World Psychiatry, vol. 15, no. 1, pp. 5–12, 2016, doi: 10.1002/wps.20292.

[4] K. S. Kendler, “Classification of psychopathology: conceptual and historical background,” World Psychiatry, vol. 17, no. 3, pp. 241–242, Oct. 2018, doi: 10.1002/wps.20549.

[5] G. V. Polanczyk, G. A. Salum, L. S. Sugaya, A. Caye, and L. A. Rohde, “Annual Research Review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents,” Journal of Child Psychology and Psychiatry, vol. 56, no. 3, pp. 345–365, 2015, doi: 10.1111/jcpp.12381.

[6] S. V. Faraone et al., “Attention-deficit/hyperactivity disorder,” Nat Rev Dis Primers, vol. 1, p. 15020, 06 2015, doi: 10.1038/nrdp.2015.20.

[7] American Psychiatric Association, Diagnostic and statistical manual of mental disorders - 5th edition. 2013.

[8] American Psychiatric Association, Diagnostic and statistical manual of mental disorders - 4th edition. 1994.

[9] R. A. Barkley and J. Biederman, “Toward a broader definition of the age-of-onset criterion for attention-deficit hyperactivity disorder,” J Am Acad Child Adolesc Psychiatry, vol. 36, no. 9, pp. 1204–1210, Sep. 1997, doi: 10.1097/00004583-199709000-00012.

[10] S. V. Faraone et al., “Diagnosing adult attention deficit hyperactivity disorder: are late onset and subthreshold diagnoses valid?,” Am J Psychiatry, vol. 163, no. 10, pp. 1720–1729; quiz 1859, Oct. 2006, doi: 10.1176/ajp.2006.163.10.1720.

[11] G. Polanczyk, A. Caspi, R. Houts, S. H. Kollins, L. A. Rohde, and T. E. Moffitt, “Implications of extending the ADHD age-of-onset criterion to age 12: results from a prospectively studied birth cohort,” J Am Acad Child Adolesc Psychiatry, vol. 49, no. 3, pp. 210–216, Mar. 2010.

[12] J. Biederman et al., “An open-label trial of OROS methylphenidate in adults with late-onset ADHD,” CNS Spectr, vol. 11, no. 5, pp. 390–396, May 2006, doi: 10.1017/s1092852900014528.

[13] M. C. Reinhardt et al., “Is age-at-onset criterion relevant for the response to methylphenidate in attention-deficit/hyperactivity disorder?,” J Clin Psychiatry, vol. 68, no. 7, pp. 1109–1116, Jul. 2007, doi: 10.4088/jcp.v68n0720.

[14] T. E. Moffitt et al., “Is Adult ADHD a Childhood-Onset Neurodevelopmental Disorder? Evidence From a Four-Decade Longitudinal Cohort Study,” Am J Psychiatry, vol. 172, no. 10, pp. 967–977, Oct. 2015, doi: 10.1176/appi.ajp.2015.14101266.

[15] J. C. Agnew-Blais, G. V. Polanczyk, A. Danese, J. Wertz, T. E. Moffitt, and L. Arseneault, “Evaluation of the Persistence, Remission, and Emergence of Attention-Deficit/Hyperactivity Disorder in Young Adulthood,” JAMA Psychiatry, vol. 73, no. 7, pp. 713–720, 01 2016, doi: 10.1001/jamapsychiatry.2016.0465.

[16] L. Riglin et al., “Association of Genetic Risk Variants With Attention-Deficit/Hyperactivity Disorder Trajectories in the General Population,” JAMA Psychiatry, vol. 73, no. 12, pp. 1285–1292, Dec. 2016, doi: 10.1001/jamapsychiatry.2016.2817.

[17] A. Caye et al., “Attention-Deficit/Hyperactivity Disorder Trajectories From Childhood to Young Adulthood: Evidence From a Birth Cohort Supporting a Late-Onset Syndrome,” JAMA Psychiatry, vol. 73, no. 7, pp. 705–712, 01 2016, doi: 10.1001/jamapsychiatry.2016.0383.

[18] S. V. Faraone and J. Biederman, “Can Attention-Deficit/Hyperactivity Disorder Onset Occur in Adulthood?,” JAMA Psychiatry, vol. 73, no. 7, pp. 655–656, 01 2016, doi: 10.1001/jamapsychiatry.2016.0400.

[19] M. H. Sibley et al., “Late-Onset ADHD Reconsidered With Comprehensive Repeated Assessments Between Ages 10 and 25,” Am J Psychiatry, p. appiajp201717030298, Oct. 2017, doi: 10.1176/appi.ajp.2017.17030298.

[20] M. Cooper et al., “Investigating late-onset ADHD: a population cohort investigation,” J Child Psychol Psychiatry, vol. 59, no. 10, pp. 1105–1113, 2018, doi: 10.1111/jcpp.12911.

[21] M. J. Taylor, H. Larsson, C. Gillberg, P. Lichtenstein, and S. Lundström, “Investigating the childhood symptom profile of community-based individuals diagnosed with attention-deficit/hyperactivity disorder as adults,” Journal of Child Psychology and Psychiatry, vol. 60, no. 3, pp. 259–266, 2019, doi: 10.1111/jcpp.12988.

[22] T. Insel et al., “Research Domain Criteria (RDoC): Toward a New Classification Framework for Research on Mental Disorders,” AJP, vol. 167, no. 7, pp. 748–751, Jul. 2010, doi: 10.1176/appi.ajp.2010.09091379.

[23] C. A. Sanislow, M. Ferrante, J. Pacheco, M. V. Rudorfer, and S. E. Morris, “Advancing Translational Research Using NIMH Research Domain Criteria and Computational Methods,” Neuron, vol. 101, no. 5, pp. 779–782, 06 2019, doi: 10.1016/j.neuron.2019.02.024.

[24] S. Kapur, A. G. Phillips, and T. R. Insel, “Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it?,” Mol. Psychiatry, vol. 17, no. 12, pp. 1174–1179, Dec. 2012, doi: 10.1038/mp.2012.105.

[25] M. P. Milham, R. C. Craddock, and A. Klein, “Clinically useful brain imaging for neuropsychiatry: How can we get there?,” Depress Anxiety, vol. 34, no. 7, pp. 578–587, 2017, doi: 10.1002/da.22627.

[26] S. E. Hyman, “Can neuroscience be integrated into the DSM-V?,” Nat. Rev. Neurosci., vol. 8, no. 9, pp. 725–732, Sep. 2007, doi: 10.1038/nrn2218.

[27] G. A. Salum, A. Gadelha, G. V. Polanczyk, E. C. Miguel, and L. A. Rohde, “Diagnostic operationalization and phenomenological heterogeneity in psychiatry: the case of attention deficit hyperactivity disorder,” Salud Mental, vol. 41, no. 6, pp. 249–259, Dec. 2018, doi: 10.17711/SM.0185-3325.2018.037.

[28] C. A. Ross and R. L. Margolis, “Research Domain Criteria: Strengths, Weaknesses, and Potential Alternatives for Future Psychiatric Research,” MNP, vol. 5, no. 4, pp. 218–236, 2019, doi: 10.1159/000501797.

[29] E. Feczko, O. Miranda-Dominguez, M. Marr, A. M. Graham, J. T. Nigg, and D. A. Fair, “The Heterogeneity Problem: Approaches to Identify Psychiatric Subtypes,” Trends Cogn. Sci. (Regul. Ed.), vol. 23, no. 7, pp. 584–601, Jul. 2019, doi: 10.1016/j.tics.2019.03.009.

[30] J. Arnedo et al., “Uncovering the hidden risk architecture of the schizophrenias: confirmation in three independent genome-wide association studies,” Am J Psychiatry, vol. 172, no. 2, pp. 139–153, Feb. 2015, doi: 10.1176/appi.ajp.2014.14040435.

[31] B. A. Clementz et al., “Identification of Distinct Psychosis Biotypes Using Brain-Based Biomarkers,” Am J Psychiatry, vol. 173, no. 4, pp. 373–384, Apr. 2016, doi: 10.1176/appi.ajp.2015.14091200.

[32] A. T. Drysdale et al., “Resting-state connectivity biomarkers define neurophysiological subtypes of depression,” Nat. Med., vol. 23, no. 1, pp. 28–38, 2017, doi: 10.1038/nm.4246.

[33] D. A. Fair, D. Bathula, M. A. Nikolas, and J. T. Nigg, “Distinct neuropsychological subgroups in typically developing youth inform heterogeneity in children with ADHD,” Proc. Natl. Acad. Sci. U.S.A., vol. 109, no. 17, pp. 6769–6774, Apr. 2012, doi: 10.1073/pnas.1115365109.

[34] J. Biederman et al., “Impact of executive function deficits and attention-deficit/hyperactivity disorder (ADHD) on academic outcomes in children,” J Consult Clin Psychol, vol. 72, no. 5, pp. 757–766, Oct. 2004, doi: 10.1037/0022-006X.72.5.757.

[35] J. T. Nigg, E. G. Willcutt, A. E. Doyle, and E. J. S. Sonuga-Barke, “Causal heterogeneity in attention-deficit/hyperactivity disorder: do we need neuropsychologically impaired subtypes?,” Biol. Psychiatry, vol. 57, no. 11, pp. 1224–1230, Jun. 2005, doi: 10.1016/j.biopsych.2004.08.025.

[36] H. R. Snyder, “Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review,” Psychol Bull, vol. 139, no. 1, pp. 81–132, Jan. 2013, doi: 10.1037/a0028727.

[37] T. Dickinson, R. Becerra, and J. Coombes, “Executive functioning deficits among adults with Bipolar Disorder (types I and II): A systematic review and meta-analysis,” J Affect Disord, vol. 218, pp. 407–427, 15 2017, doi: 10.1016/j.jad.2017.04.010.

[38] N. F. Forbes, L. A. Carrick, A. M. McIntosh, and S. M. Lawrie, “Working memory in schizophrenia: a meta-analysis,” Psychol Med, vol. 39, no. 6, pp. 889–905, Jun. 2009, doi: 10.1017/S0033291708004558.

[39] M. F. Green, “What are the functional consequences of neurocognitive deficits in schizophrenia?,” Am J Psychiatry, vol. 153, no. 3, pp. 321–330, Mar. 1996, doi: 10.1176/ajp.153.3.321.

[40] S. Shanmugan et al., “Common and Dissociable Mechanisms of Executive System Dysfunction Across Psychiatric Disorders in Youth,” Am J Psychiatry, vol. 173, no. 5, pp. 517–526, 01 2016, doi: 10.1176/appi.ajp.2015.15060725.

[41] A. F. Klassen, A. Miller, and S. Fine, “Health-related quality of life in children and adolescents who have a diagnosis of attention-deficit/hyperactivity disorder,” Pediatrics, vol. 114, no. 5, pp. e541-547, Nov. 2004, doi: 10.1542/peds.2004-0844.

[42] A. W. Tolman and M. M. Kurtz, “Neurocognitive predictors of objective and subjective quality of life in individuals with schizophrenia: a meta-analytic investigation,” Schizophr Bull, vol. 38, no. 2, pp. 304–315, Mar. 2012, doi: 10.1093/schbul/sbq077.

[43] P. M. Wehmeier, A. Schacht, and R. A. Barkley, “Social and emotional impairment in children and adolescents with ADHD and the impact on quality of life,” J Adolesc Health, vol. 46, no. 3, pp. 209–217, Mar. 2010, doi: 10.1016/j.jadohealth.2009.09.009.

[44] T. E. Moffitt et al., “A gradient of childhood self-control predicts health, wealth, and public safety,” Proc. Natl. Acad. Sci. U.S.A., vol. 108, no. 7, pp. 2693–2698, Feb. 2011, doi: 10.1073/pnas.1010076108.

[45] R. C. K. Chan, D. Shum, T. Toulopoulou, and E. Y. H. Chen, “Assessment of executive functions: review of instruments and identification of critical issues,” Arch Clin Neuropsychol, vol. 23, no. 2, pp. 201–216, Mar. 2008, doi: 10.1016/j.acn.2007.08.010.

[46] D. A. Robson, M. S. Allen, and S. J. Howard, “Self-regulation in childhood as a predictor of future outcomes: A meta-analytic review,” Psychol Bull, Jan. 2020, doi: 10.1037/bul0000227.

[47] A. Pandey, D. Hale, S. Das, A.-L. Goddings, S.-J. Blakemore, and R. M. Viner, “Effectiveness of Universal Self-regulation-Based Interventions in Children and Adolescents: A Systematic Review and Meta-analysis,” JAMA Pediatr, vol. 172, no. 6, pp. 566–575, 01 2018, doi: 10.1001/jamapediatrics.2018.0232.

[48] G. A. Salum et al., “High risk cohort study for psychiatric disorders in childhood: rationale, design, methods and preliminary results,” Int J Methods Psychiatr Res, vol. 24, no. 1, pp. 58–73, Mar. 2015, doi: 10.1002/mpr.1459.

[49] A. Caspi et al., “The p Factor: One General Psychopathology Factor in the Structure of Psychiatric Disorders?,” Clin Psychol Sci, vol. 2, no. 2, pp. 119–137, Mar. 2014, doi: 10.1177/2167702613497473.

[50] B. B. Lahey, R. F. Krueger, P. J. Rathouz, I. D. Waldman, and D. H. Zald, “Validity and utility of the general factor of psychopathology,” World Psychiatry, vol. 16, no. 2, pp. 142–144, Jun. 2017, doi: 10.1002/wps.20410.

[51] P. Asherson and J. Agnew-Blais, “Annual Research Review: Does late-onset attention-deficit/hyperactivity disorder exist?,” Journal of Child Psychology and Psychiatry, vol. 60, no. 4, pp. 333–352, 2019, doi: 10.1111/jcpp.13020.

[52] E. J. S. Sonuga-Barke, “Editorial: ‘People get ready’: Are mental disorder diagnostics ripe for a Kuhnian revolution?,” Journal of Child Psychology and Psychiatry, vol. 61, no. 1, pp. 1–3, 2020, doi: 10.1111/jcpp.13181.

7. ANEXOS

Outros Artigos Publicados Durante o Período do Doutorado

Artigo Anexo #1 (Resumo)

Publicado no European Child and Adolescent Psychiatry

Psychopathology and Friendship in Children and Adolescents: Disentangling the Role of Co-Occurring Symptom Domains With Serial Mediation Models

Arthur Gus Manfro, Pedro M Pan, Ary Gadelha, Marcelo Fleck, Maria C do Rosário, Hugo Cogo-Moreira, Rodrigo Affonseca-Bressan, Jair Mari, Euripedes C Miguel, Luis A Rohde, Giovanni A Salum

DOI: 10.1007/s00787-017-0993-z

The consolidation of social friendship groups is a vital part of human development. The objective of this study is to understand the direct and indirect influences of three major symptomatic domains-emotional, hyperkinetic, and conduct-on friendship. Specifically, we aim to study if the associations of one domain with friendship may be mediated by co-occurring symptoms from another domain. A total of 2512 subjects aged 6-14 years participated in this study. Friendship was evaluated by the Development and Well-Being Assessment's friendship section. We evaluated two main constructs as outcomes: (1) social isolation and (2) friendship latent construct. Emotional, hyperkinetic, and conduct symptomatic domains were evaluated with the Strengths and Difficulties Questionnaire (SDQ). All SDQ domains were positively associated with social isolation and negatively associated with friendship latent construct in univariate analysis. However, serial mediation models showed that the association between conduct domains with social isolation was mediated by emotion and hyperkinetic domains. Moreover, the associations between emotional and hyperkinetic domains with friendship latent construct in non-isolated children were mediated by the conduct domain. Emotion and hyperkinetic domains were directly and indirectly associated with social isolation, whereas conduct was directly and indirectly associated with overall friendship in non-isolated children. Results suggest that interventions aimed to improve social life in childhood and adolescence may have stronger effects if directed towards the treatment of emotion and hyperkinetic symptoms in socially isolated children and directed towards the treatment of conduct symptoms in children with fragile social connections.

Keywords: Friendship; Mediation; Psychopathology.

Artigo Anexo #2 (Resumo)

Publicado na Trends in Psychiatry and Psychotherapy

Brazilian Portuguese Version of the Anger Rumination Scale (ARS-Brazil)

Daniela Sperotto, Arthur Gus Manfro, Luiza Kvitko Axelrud, Pedro Henrique Manfro, Giovanni Abrahão Salum, Diogo Araújo DeSousa

DOI: 10.1590/2237-6089-2017-0026

Objective: To describe the cross-cultural adaptation of the Anger Rumination Scale (ARS) for use in Brazil. Methods: The cross-cultural adaptation followed a four-step process, based on specialized literature: 1) investigation of conceptual and item equivalence; 2) translation and back-translation; 3) pretest; and 4) investigation of operational equivalence. Results: A final Brazilian version of the instrument (ARS-Brazil) was defined and is presented. Pretest results revealed that the instrument was generally well understood by adults as well as indicated a few modifications that were included in the final version presented here. Conclusion: The Brazilian Portuguese version of the ARS seems to be very similar to the original ARS in terms of conceptual and item equivalence, semantics, and operational equivalence, suggesting that future cross-cultural studies may benefit from this early version. As a result, a new instrument is now available for the assessment of rumination symptoms of anger and irritability for adults in community, clinical, and research settings.

Artigo Anexo #3 (Resumo)

Publicado no Attention Deficit and Hyperactivity Disorder

Reaction Time Variability and Attention-Deficit/Hyperactivity Disorder: Is Increased Reaction Time Variability Specific to Attention-Deficit/Hyperactivity Disorder? Testing Predictions From the Default-Mode Interference Hypothesis

Giovanni A Salum, João R Sato, Arthur G Manfro, Pedro M Pan, Ary Gadelha, Maria C do Rosário, Guilherme V Polanczyk, Francisco X Castellanos, Edmund Sonuga-Barke, Luis A Rohde

DOI: 10.1007/s12402-018-0257-x

Increased reaction time variability (RTV) is one of the most replicable behavioral correlates of attention-deficit/hyperactivity disorder (ADHD). However, this may not be specific to ADHD but a more general marker of psychopathology. Here we compare RT variability in individuals with ADHD and those with other childhood internalizing and externalizing conditions both in terms of standard (i.e., the standard deviation of reaction time) and alternative indices that capture low-frequency oscillatory patterns in RT variations over time thought to mark periodic lapses of attention in ADHD. A total of 667 participants (6-12 years old) were classified into non-overlapping diagnostic groups consisting of children with fear disorders (n = 91), distress disorders (n = 56), ADHD (n = 103), oppositional defiant or conduct disorder (ODD/CD; n = 40) and typically developing controls (TDC; n = 377). We used a simple two-choice reaction time task to measure reaction time. The strength of oscillations in RTs across the session was extracted using spectral analyses. Higher RTV was present in ADHD compared to all other disorder groups, effects that were equally strong across all frequency bands. Interestingly, we found that lower RTV to characterize ODD/CD relative to TDC, a finding that was more pronounced at lower frequencies. In general, our data support RTV as a specific marker of ADHD. RT variation across time in ADHD did not show periodicity in a specific frequency band, not supporting that ADHD RTV is the product of spontaneous periodic lapses of attention. Low-frequency oscillations may be particularly useful to differentiate ODD/CD from TDC.

Keywords: Attentional lapses; Conduct disorder; Oppositional defiant disorder; Reaction time variability; State regulation.

Artigo Anexo #4 (Resumo)

Publicado no Journal of the American Academy of Child and Adolescent Psychiatry

Relative Age and Attention-Deficit/Hyperactivity Disorder: Data From Three Epidemiological Cohorts and a Meta-Analysis

Arthur Caye, Sandra Petresco, Aluísio Jardim Dornellas de Barros, Rodrigo A Bressan, Ary Gadelha, Helen Gonçalves, Arthur Gus Manfro, Alícia Matijasevich, Ana Maria Baptista Menezes, Euripides C Miguel, Tiago Neuenfeld Munhoz, Pedro M Pan, Giovanni A Salum, Iná S Santos, Christian Kieling, Luis Augusto Rohde

DOI: 10.1016/j.jaac.2019.07.939

Objective: To investigate the effect of relatively younger age on Attention-deficit/hyperactivity disorder (ADHD) symptoms and diagnosis through three population-based cohorts and a meta-analysis.

Method: Individuals included in this study were participants of three community-based cohorts in Brazil: the 1993 Pelotas Cohort (N=5,249), the 2004 Pelotas Cohort (N=4,231), and the Brazilian High-Risk Study for Psychiatric disorders (HRC study, N=2,511). We analyzed the effect of relatively younger age on ADHD symptoms and diagnosis. For the meta-analysis, we searched MEDLINE, PsycINFO, and Web of Science from inception through December 25th, 2018. We selected studies that reported measures of association between relative immaturity and an ADHD diagnosis. We followed the Meta-analysis of Observational Studies in Epidemiology guidelines. The protocol for meta-analysis is available on PROSPERO (CRD42018099966).

Results: In the meta-analysis, we identified 1,799 potentially eligible records, from which 25 studies including 8,076,570 individuals (164,049 ADHD cases) were analyzed with their effect estimates. The summarized relative risk of an ADHD diagnosis was 1.34 (95% Confidence Interval, 1.26 to 1.43, p <.001) for children born in the first four months of the school year (relatively younger). Heterogeneity was high (I2 = 96.7%). Relative younger age was associated with higher levels of ADHD symptoms in the 1993 Pelotas cohort (p=.003), in the 2004 Pelotas cohort (p=.046) and in the HRC study (p=.010).

Conclusion: Children and adolescents who are relatively younger compared to their classmates have a higher risk of receiving an ADHD diagnosis. Clinicians should consider the developmental level of young children when evaluating ADHD symptoms.

Keywords: ADHD; development; immaturity; relative age.