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ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

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Characteristics and Predictors of Fluctuating Attention-Deficit/Hyperactivity Disorder in the Multimodal Treatment of ADHD (MTA) Study

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Abstract

Objectives: Recent studies report a fluctuating course of attention-deficit/ hyperactivity disorder (ADHD) across development characterized by intermittent periods of remission and recurrence. In the Multimodal Treatment of ADHD (MTA) study, we investigated fluctuating ADHD including clinical expression over time, childhood predictors, and between- and within-person associations with factors hypothesized as relevant to remission and recurrence

The fluctuating subgroup (63.8% of sample) was compared to other MTA subgroups on variables of interest over time.

Results: The fluctuating subgroup experienced multiple fluctuations over 16 years (mean = 3.58, SD = 1.36) with a 6- to 7-symptom within-person difference between peaks and troughs. Remission periods typically first occurred in adolescence and were associated with higher environmental demands (both between- and within-person), particularly at younger ages. Compared to other groups, the fluctuating subgroup demonstrated moderate clinical severity. In contrast, the stable persistent group (10.8%) was specifically associated with early and lasting risk for mood disorders, substance use problems in adolescence/ young adulthood, low medication utilization, and poorer response to childhood treatment. Protective factors were detected in the recovery group (9.1%; very low parental psychopathology) and the partial remission group (15.6%; higher rates of comorbid anxiety).

Conclusions: In the absence of specific risk or protective factors, individuals with ADHD demonstrated meaningful within-individual fluctuations across development. Clinicians should communicate this expectation and monitor fluctuations to trigger as-needed return to care. During remission periods, individuals with ADHD successfully manage increased demands and responsibilities.

Trial Registration: ClinicalTrials.gov identifier: NCT00000388

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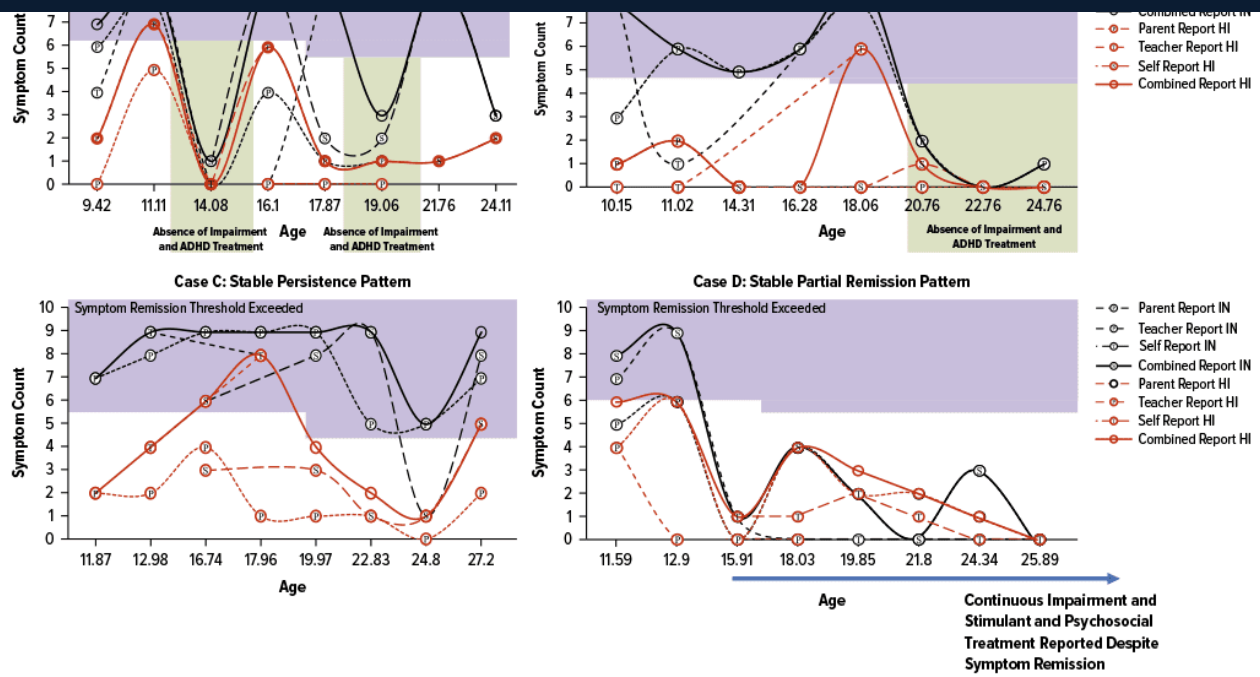
See commentary by Surman and Wilens

studies detected a fluctuating course of ADHD, challenging the notion that childhood ADHD either permanently remits or persists in adulthood.[2–6] These studies raise a possibility that ADHD is trait-like and waxing and waning (like hypertension or obesity)[7]; still, the nature of fluctuating ADHD remains poorly understood.

In the Multimodal Treatment of ADHD (MTA) long term follow-up,[5] fluctuating ADHD occurred in 63.8% of the sample, characterized by alternating periods of remission and recurrence. Yet, the detailed experiences of fluctuating cases remain uncharacterized, including determinants of stable vs fluctuating ADHD. Childhood factors distinguishing endpoint-defined persistent vs remitted ADHD are numerous and include demographic, clinical (eg, childhood symptoms, comorbidities), and contextual factors (eg, parenting, negative events, psychosocial risks).[8–10] However, these variables may not be predictive of varying courses of ADHD (stable persistent ADHD, stable partial remission, recovery, fluctuating; see Figure 1).[5]



[a]For a full description of full remission, partial remission, and persistence criteria, see Supplementary Appendix 3. In Sibley et al,[5] we defined a fluctuating pattern (Case A) as demonstrating at least 2 changes to cross-sectional classification since baseline diagnosis of ADHD, in the absence of the recovery pattern. Recovery (Case B) was untreated full remission of ADHD that persisted for at least 2 consecutive assessments without being followed by an episode of recurrence (ie, full remission continued until study endpoint). Individuals were classified as displaying stable persistence (Case C) if they demonstrated persistent ADHD for all assessments to date in the follow-up period. Stable partial remission (Case D) was defined as displaying 1 classification change from persistent ADHD to partial remission that maintained until study endpoint. Despite smoothed lines, symptom levels between assessment points are unknown.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, HI = hyperactivity/impulsivity, IN = inattention.

Since ADHD often fluctuates, the field also must begin investigating variables that trigger symptom exacerbation and abatement (ie, do changes to one's environment coincide with the onset of a fluctuation?). Some research suggests that ADHD severity intensifies under increased executive function burden.[11,12] Other work suggests that adults with ADHD perceive that their symptoms are best managed in demanding, fast-paced, and stimulating environments.[13,14] Such mixed findings indicate a need for complex analyses that model individual differences in remission (eg, disaggregating between- vs within-person trends), model bidirectionality, and moderators of effects and consider nonlinear relations in the data. Clarifying factors that predict ADHD course and fluctuations may signal novel person-specific intervention targets.

This study provides detailed comparison of the MTA's fluctuating ADHD

utilize treatment over time and (2) differ on childhood risk factors. Among fluctuators, we evaluate whether periods of remission/recurrence coincide with level of environmental demands and whether these relations are moderated by age. We expect new distal childhood predictors to emerge using longitudinal subgroups[10] and hypothesize that fluctuators experiencing higher demands (across assessments) will be more likely to demonstrate remission periods (between-person effect) due to increased capacity for demanding environments; however, when demands are higher than usual for an individual (within-person effect), occurrence of ADHD will be more likely due to increased cognitive load.[11]

METHODS

The MTA[16] originally compared 14-month pharmacological and behavioral treatments for 579 children (7.0–9.9 years old) with *DSM-IV* ADHD, combined type. Baseline characteristics are in Supplementary Table 1. The MTA continued for 14 additional years with prospective follow-ups approximately biennially (8 assessments) until 16 years after baseline.[17–20]

Participants

The current subsample (N = 483; 83.4% of original sample) includes participants with ADHD who had at least 1 follow-up assessment in adulthood (age 18 or older).

Procedures

Assessments were administered to participants and parents at baseline and 2-, 3-, 6-, 8-, 10-, 12-, 14-, and 16- years postbaseline by closely supervised bachelor's-level staff. Teacher ratings were

Measures

ADHD symptoms. Child and adolescent symptoms were measured using the parent, teacher, and self-reported SNAP.[21,22] Adult symptoms were measured using the parent- and self-report Conners Adult ADHD Rating Scale (CAARS).[23] Both instruments measure *DSM-IV-TR* ADHD symptoms rated 0 (not at all) to 3 (very much). Scores of 2–3 on individual *DSM-IV-TR* symptoms indicated symptom presence.[24]

Impairment. In childhood and adolescence, impairment was measured using the parent-report Columbia Impairment Scale (CIS), which assesses 13 impairment domains on a 0–4 scale.[25,26] In adulthood, the parent- and self-report Impairment Rating Scale (IRS) measured impairment globally and in eleven domains from 0=no problem to 6=extreme problem.[27] Supplementary Appendix 1 describes impairment thresholding.

Mental health and substance use disorders. The Diagnostic Interview Schedule for Children (DISC)[28] was administered via parent- and self-reports. Self-report began at the 6-year follow-up; the DISC was not administered at the 10-year follow-up. The DISC is a structured interview querying the presence of *DSM* criteria using screening questions and supplemental probes. Supplementary Appendix 1 lists included disorders. At each assessment, a comorbidity index was calculated by summing the total number of current diagnoses across reporters.[10]

Service utilization. The Services for Children and Adolescents Parent Interview[29] was administered through the 10-year assessment. It assesses between-assessment estimates of daily dose and number of days treated for ADHD medications, as well as psychosocial and educational interventions, including frequency, duration, and type of

Distal childhood predictors. We used a set of childhood predictors similar to those previously examined in several longitudinal MTA analyses.[10,31] These included baseline age, sex, race/ethnicity, parent- and teacher-rated ADHD symptom severity, a biological risk score reflecting pre and perinatal risks,[32] a psychosocial risk index,[33] parental psychopathology, alcohol use disorder, maternal depression, childhood physical health, childhood mental health, ODD/CD, anxiety and mood disorder diagnoses, dimensionally measured anxiety and depression, negative life events, full scale IQ, continuous performance test scores,[34] initial randomized treatment group, response to initial randomized treatment (regardless of treatment group) at 36 months, [31] prestudy medication, psychosocial treatment, and educational interventions, extracurricular activities, negative/ineffective parental discipline and positive parenting,[35] and number of close friends. See Supplementary Appendix 2 for details about measurement of predictors.

Environmental demands. Based on available information at each assessment, environmental demands were coded at 6 adolescent/adult time points to reflect demands level across responsibilities domains. Points were aggregated for living situation (1=independent and 0= with adult caregivers), financial responsibility (1=full, 0.5=partial, and 0=dependent), employment (1=full work week, 0.5=partial work week, and none=0), and educational enrollment (1=full time student, 0.5=part time student, and 0=none) and has child(ren) (1=yes and 0=no).

Analytic Plan

Per Sibley et al,[5] at each time point, participants were classified as fully remitted, partially remitted, or persistent ADHD considering symptom level, impairment, treatment utilization, and other disorders that better

hyperactivity/impulsivity [HI]) according to all informants, absence of clinically significant impairment, and discontinuation of all ADHD intervention for at least a month prior to assessment. For persistent, we utilized a previously validated definition of persistence, which applied the *DSM-5* symptom threshold (5 or 6 symptoms of either inattention or hyperactivity/impulsivity, depending on age) using the CAARS (or SNAP) and impairment threshold of "3 or higher" on the IRS (or CIS). Partially remitted cases met criteria for neither persistence nor full remission, typically because they had low symptoms but continued impairment, high symptoms but insufficient impairment, or met symptom and impairment criteria for full remission, but were currently treated. After classifying each participant's cross-sectional remission status at each assessment, participants were classified into 4 longitudinal subgroups (fluctuating, stable persistence, stable partial remission, recovery; Figure 1).

Aim 1: characterize MTA longitudinal patterns of remission. Within each longitudinal subgroup, we examined rates of study endpoint-defined *DSM-5* ADHD symptom persistence vs remission.[15] We then calculated the average number of fluctuations, IN and HI symptom peak and trough count, age of first remission (partial or full), proportion of assessments with impairment, proportion of assessments receiving medication, and proportion of assessments receiving psychosocial treatment. General linear models were used to compare longitudinal remission status on each index. Cohen *d* and relative risk were calculated for continuous and categorical variables, respectively.

Aim 2: relations between childhood variables and longitudinal patterns of remission. For continuous childhood variables, general linear models examined associations between longitudinal remission pattern and each childhood variable. Six planned comparisons (comparing each

Benjamini-Hochberg false discovery rate correction was applied at the omnibus test level within domain (eg, comorbidity) and separately across planned paired comparisons.[36] Cohen *d* and relative risk were calculated as described for Aim 1.

Aim 3: relations between environmental demands and ADHD fluctuations. Within the fluctuating group (n=335), using data from the 6 through 16-year follow-ups, we conducted a multilevel multinomial logistic regression with random intercepts and time-varying ADHD remission status (0=full remission, 1=partial remission, 2=persistent) as the outcome variable. A time-varying grand mean-centered age variable was included in the model as a covariate. We tested the effect of environmental demands on ADHD remission status and disaggregated within-person and between-person effects[37,38] by modeling both a between-person environmental demands predictor (centered at the sample mean) and a within-person, time varying environmental demands predictor (centered at each subject's individual mean across time).[39,40] We also included an age×time-varying environmental demands interaction term to examine whether the effect of environmental demands on ADHD remission status varies by the person's age. For this model, we used all available data from participants, with each participant on average contributing 5.04/6 possible data points (83.5% complete data). In a model with fewer datapoints, we also explored robustness of results to covarying comorbidity (see Supplementary Appendix 4). Analyses were conducted in SPSS 29.0 using the GENLINMIXED procedure and a logit link function.

RESULTS

Characterize MTA Longitudinal Patterns of Remission

and 80.1% fluctuating. The endpoint symptom remission subgroup[15] consisted of the following longitudinal patterns: 22.0% recovery, 15.7% sustained partial remission, 0.0% stable persistence, and 62.3% fluctuating. Similar proportions of longitudinal fluctuators met criteria for ADHD symptom persistence (56.6%) and remission (43.4%) at MTA endpoint.

With few exceptions (see Table 1), longitudinal subgroups significantly differed from one another on all clinical variables. Because there were significant differences between groups in terms of number of assessments completed, we conducted sensitivity analyses restricting the sample to only those participants with 6 or more assessment points, which resulted in very minimal changes in the results reported below (see Supplementary Table 4).

Table 1.
Group Differences in ADHD Symptoms, Impairment, and Treatment Utilization Patterns[a]

	1. Fluctuating, mean (SD) N = 335	2. Stable persistence, mean (SD) N = 37	3. Stable partial remission, mean (SD) N = 60	4. Recovery, mean (SD) N = 51	*P* value						Effect size					
					1 vs 2	1 vs 3	1 vs 4	2 vs 3	2 vs 4	3 vs 4	1 vs 2	1 vs 3	1 vs 4	2 vs 3	2 vs 4	3 vs 4
Total fluctuations	3.58 (1.36)	0.00 (0.00)	1.00 (0.00)	3.11 (1.19)	**<.001**	**<.001**	**.011**	**<.001**	**<.001**	**<.001**	2.92	2.24	0.35	—	−4.51	−3.86
In count peak	8.47 (1.24)	8.81 (0.62)	7.63 (2.66)	6.94 (2.62)	.233	**<.001**	**<.001**	**<.001**	**<.001**	**.027**	−0.29	0.58	1.08	0.63	1.05	0.26
H/I count peak	7.01 (2.22)	8.11 (1.49)	6.33 (2.68)	5.04 (2.65)	**.006**	**.034**	**<.001**	**<.001**	**<.001**	**.003**	−0.51	0.30	0.87	0.80	1.42	0.48
In count trough	1.32 (1.89)	5.95 (1.98)	0.88 (1.22)	0.06 (0.31)	**<.001**	.072	**<.001**	**<.001**	**<.001**	**.012**	−2.44	0.25	0.75	3.36	5.82	1.02
H/I count trough	0.97 (1.38)	3.54 (2.59)	0.78 (1.12)	0.16 (0.46)	**<.001**	.354	**<.001**	**<.001**	**<.001**	**.020**	−1.71	0.14	0.64	1.64	2.49	0.76
Age at first remission episode	12.52 (3.63)	—	18.87 (5.81)	11.72 (2.69)	—	**<.001**	.175	—	—	**<.001**	—	−1.60	0.23	—	—	1.63
Proportion of assessments impaired (%)	82.60 (19.96)	100.00 (0.00)	89.50 (18.55)	44.83 (21.06)	**<.001**	**.014**	**<.001**	**.010**	**<.001**	**<.001**	−0.97	−0.35	1.88	0.92	1.15	2.27
Proportion of assessments with comorbidity (%)																
Anxiety	17.26 (17.36)	25.00 (23.82)	25.29 (25.04)	12.60 (16.87)	**.019**	**.003**	.102	.942	**.003**	**<.001**	−0.43	−0.43	0.27	0.01	0.63	0.60
Mood	4.30 (8.81)	12.98 (17.94)	6.94 (11.96)	1.55 (5.00)	**<.001**	.059	**<.001**	**.004**	**<.001**	**.005**	−0.89	−0.28	0.33	0.42	1.09	0.62
Substance use[b]	27.32 (30.68)	33.84 (34.35)	24.33 (32.68)	11.27 (20.23)	.221	.482	**<.001**	.137	**<.001**	**.024**	−0.21	0.10	0.55	0.29	0.86	0.48
Proportion of assessments medicated (%)	30.10 (25.42)	21.53 (26.42)	33.89 (29.91)	20.19 (19.54)	.052	.308	**.010**	**.023**	.808	**.006**	0.34	−0.15	0.40	−0.61	0.06	0.54
Proportion of assessments with psychosocial treatment (%)	20.74 (22.30)	34.44 (27.65)	38.11 (28.96)	8.94 (12.74)	**<.001**	**<.001**	**<.001**	.461	**<.001**	**<.001**	−0.58	−0.75	0.56	−0.13	1.34	1.36
Number of assessments	6.93 (1.56)	5.97 (2.47)	5.10 (2.59)	7.27 (1.11)	**<.001**	**<.001**	.199	**.018**	**<.001**	**<.001**	0.58	1.07	−0.23	0.34	−0.77	−1.14
***DSM-5* symptom persistence at adult endpoint (%)**	56.6	100.00	22.2	0.00	**<.001**	**<.001**	**<.001**	**<.001**	**<.001**	**<.001**	*0.57*	*2.55*	—	*4.50*	—	—
Age at final assessment (years)	24.75 (1.51)	24.58 (2.13)	24.37 (1.98)	24.79 (1.62)	.559	.094	.859	.523	.554	.170	0.11	0.24	−0.03	0.10	−0.11	−0.23

[a]We defined recovery as full remission of ADHD sustained for at least 2 consecutive assessments without a subsequent recurrence (full remission until study endpoint). Stable persistence was persistent ADHD over the entire follow-up. A fluctuating pattern was defined by at least 2 changes to classification since baseline diagnosis of ADHD, in the absence of the recovery pattern. Stable partial remission was defined as displaying 1 classification change from persistent ADHD to partial remission that continued until study endpoint. Effect sizes are Cohen *d* standardized mean difference scores except for symptom persistence classification, which reflects relative risk; relative risk calculations denoted in italics. Boldface indicates statistical significance.
[b]Information on substance use disorders was gathered only at the 6 through 16-year assessments.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, H/I = hyperactivity/impulsivity.

The fluctuating group (N = 335; see Table 1) was characterized by the most ADHD classification changes over time (mean = 3.58, SD = 1.36), high ADHD symptom peaks paired with low troughs (~6–7 symptom difference), average first remission in early adolescence (mean = 12.52, SD = 3.63), relatively stable impairment, and relatively moderate

The stable persistent group (N = 37) was characterized by no ADHD classification changes, high ADHD symptom peaks and troughs (~2–4 symptom difference), relatively high and stable impairment, comorbidity, and substance use rates over time, relatively low medication use, and relatively high rates of psychosocial treatment utilization over time.

The stable partial remission group (N = 60) demonstrated one classification change (from ADHD to partially remitted), which occurred in adulthood on average (mean = 18.87, SD = 5.81). They exhibited a relatively high ADHD symptom peak paired with a low trough (~6–7 symptom difference), relatively high levels of impairment, anxiety disorders, psychosocial treatment, and medication use, and relatively moderate incidence of mood and substance use disorders over time.

The recovery group (N=51) typically demonstrated several classification changes (mean=3.11, SD=1.19) prior to onset of sustained full remission, relatively moderate ADHD symptom peaks and very low symptom troughs (~5–7 symptom difference), average first period of remission occurring in childhood (mean=11.72, SD=2.69), and relatively low levels of impairment, comorbidity/substance use, and treatment utilization over time.

Childhood Predictors of Longitudinal Remission Patterns

See Table 2 for results. After applying the false discovery rate correction, parent SCID diagnoses, childhood mood disorder, childhood depression severity, and 36-month MTA treatment response predicted longitudinal subgroups. The fluctuating and stable persistence subgroups had more parent SCID diagnoses at baseline than the recovery subgroup. The fluctuating, stable remission, and

previously reported by Swanson et al,[31] the fluctuating subgroup (and recovery subgroup) had a response pattern that was significantly more favorable than the stable persistent subgroup (see Supplementary Table 2 for details). Sensitivity analyses indicated no changes in significant results using the restricted sample of participants with 6 or more datapoints.

Table 2.
Longitudinal Group Differences on Baseline and Childhood Risk and Protective Factors[a]

	1. Fluctuating N = 335	2. Stable persistence N = 37	3. Stable partial remission N = 60	4. Recovery N = 51	Omnibus effect	*P*	Effect size 1 vs 2	1 vs 3	1 vs 4	2 vs 3	2 vs 4	3 vs 4
Age at study entry, mean (SD)	8.46 (0.88)	8.66 (0.75)	8.39 (0.69)	8.47 (0.86)	F (3,479) = 0.82	.482	−0.23	0.08	−0.01	0.38	0.23	−0.10
Male sex, % (n)	78.5 (263)	73.0 (27)	80.0 (48)	78.4 (40)	χ^{23} = 0.73	.867	*1.07*	*0.98*	*1.00*	*0.91*	*0.93*	*1.02*
Racial/ethnic minority, % (n)	36.7 (123)	32.4 (12)	41.7 (25)	37.3 (19)	χ^{218} = 15.62	.619	*1.13*	*0.88*	*0.98*	*0.78*	*0.87*	*1.12*
Biological risk score,[b] mean (SD)	1.27 (1.17)	1.05 (1.08)	1.10 (0.98)	1.18 (1.05)	F (3,476) = 0.70	.551	0.19	0.15	0.08	−0.05	−0.12	−0.08
Psychosocial risk score,[c] mean (SD)	1.10 (0.84)	1.05 (0.88)	1.10 (0.77)	1.14 (0.80)	F (3,479) = 0.07	.975	0.06	0.00	−0.05	−0.06	−0.11	−0.05
Parental psychopathology												
SCID diagnoses, mean (SD)[d]	1.25 (1.51)	1.45 (1.66)	0.83 (1.03)	0.51 (0.65)	F (3,456) = 5.40	.001	−0.13	0.29	**0.53**	0.49	**0.87**	0.37
Maternal BDI score, mean (SD)	6.67 (6.10)	7.53 (6.78)	7.52 (6.74)	5.30 (5.37)	F (3,442) = 1.28	.280	−0.14	−0.14	0.23	0.00	0.37	0.36
Parental alcohol disorder, % (n)	18.1 (58)	30.3 (10)	12.1 (7)	12.2 (6)	χ^{23} = 5.92	.115	*0.60*	*1.50*	*1.50*	*2.50*	*2.48*	*0.99*
ADHD severity, mean (SD)												
Parent: SNAP inattention	2.05 (0.61)	2.30 (0.55)	2.07 (0.55)	1.91 (0.71)	F (3,479) = 2.86	.036	−0.41	−0.03	0.022	0.42	0.61	0.26
Parent: SNAP hyperactivity/impulsivity	1.89 (0.64)	1.95 (0.67)	1.88 (0.66)	1.72 (0.70)	F (3,479) = 1.25	.291	−0.09	0.02	0.26	0.11	0.33	0.24
Teacher: SNAP inattention	2.21 (0.68)	2.34 (0.61)	2.29 (0.55)	2.20 (0.64)	F (3,448) = 0.26	.855	−0.19	−0.12	0.01	0.09	0.22	0.15
Teacher: SNAP hyperactivity/impulsivity	1.98 (0.73)	1.74 (0.82)	1.98 (0.71)	1.84 (0.85)	F (3,448) = 1.52	.210	0.32	0.00	0.17	−0.32	−0.12	0.18
Child comorbidities												
Medical diagnoses, mean (SD)	0.67 (0.80)	0.76 (0.76)	0.70 (0.81)	0.61 (0.92)	F (3,477) = 0.27	.847	−0.11	−0.04	0.07	0.08	0.18	0.10
Mental health diagnoses, mean (SD)	1.70 (1.80)	2.30 (2.59)	1.70 (1.70)	1.63 (1.70)	F (3,479) = 1.26	.289	−0.32	−0.00	0.04	0.29	0.32	0.04
ODD/CD, % (n)	40.1 (129)	55.6 (20)	37.3 (22)	44.9 (22)	χ^{23} = 3.87	.276	*0.72*	*1.08*	*0.89*	*1.49*	*1.24*	*0.83*
Anxiety disorder, % (n)	38.8 (130)	45.9 (17)	40.0 (24)	37.3 (19)	χ^{23} = 0.82	.845	*0.83*	*0.97*	*1.04*	*1.15*	*1.23*	*1.07*
Mood disorder, % (n)[d]	4.5 (15)	18.9 (7)	1.7 (1)	2.0 (1)	χ^{23} = 17.78	<.001	***0.24***	*2.65*	*2.25*	***11.12***	***9.45***	*0.85*
MASC total score, mean (SD)	2.52 (0.53)	2.62 (0.55)	2.55 (0.59)	2.39 (0.52)	F (3,449) = 1.49	.216	−0.19	−0.06	0.25	0.12	0.43	0.29
CDI total score, mean (SD)[d]	0.39 (0.32)	0.39 (0.32)	0.49 (0.33)	0.30 (0.25)	F (3,476) = 3.56	.014	0.00	−0.31	0.29	−0.31	0.32	**0.65**
Negative life events, mean (SD)	3.35 (2.34)	2.92 (2.06)	3.21 (2.32)	2.78 (1.87)	F (3,474) = 1.18	.317	0.19	0.06	0.25	−0.13	0.07	0.20
IQ, mean (SD)	101.96 (14.78)	101.08 (13.22)	101.84 (13.11)	101.88 (16.38)	F (3,474) = 8.49	.989	0.06	0.01	0.01	−0.06	−0.05	0.00
CPT performance, mean (SD)												
Omission	6.87 (6.41)	5.59 (5.71)	5.63 (4.41)	5.65 (5.08)	F (3,458) = 1.40	.243	0.15	0.20	0.20	0.00	−0.01	0.00
Commission	29.07 (22.43)	25.62 (26.29)	41.91 (52.09)	28.86 (34.37)	F (3,458) = 2.33	.074	0.15	−0.48	0.01	−0.39	−0.10	0.30
Reaction time *M*	549.72 (114.84)	534.78 (106.34)	517.68 (114.61)	557.59 (145.60)	F (3,458) = 1.45	.227	0.13	0.28	−0.07	0.15	−0.18	−0.31
Reaction time *SD*	216.34 (77.58)	209.32 (67.40)	213.55 (78.90)	208.76 (72.36)	F (3,458) = 0.21	.888	0.09	0.04	0.10	−0.06	0.01	0.06
Assigned treatment group,[e] % (n)					χ^{29} = 3.69	.930						
Combined	27.2 (91)	27.0 (10)	21.7 (13)	25.5 (13)								
Medication management	22.7 (76)	27.0 (10)	28.3 (17)	25.5 (13)								
Behavioral	27.2 (91)	24.3 (9)	20.0 (12)	25.4 (13)								
Community control	23.0 (77)	21.6 (8)	30.0 (18)	23.5 (12)								
36 months treatment response,[e] % (n)[d]					χ^{26} = 18.81	.005						
Class 1: gradual improvement	33.7 (113)	45.9 (17)	41.7 (25)	23.5 (12)								
Class 2: large initial w/ maintenance	54.0 (181)	27.0 (10)	45.0 (27)	68.6 (35)								
Class 3: large initial w/ return to baseline	12.2 (41)	27.0 (10)	13.3 (8)	7.8 (4)								
Prestudy medication, % (n)	22.7 (76)	21.6 (8)	28.3 (17)	17.6 (9)	χ^{23} = 1.85	.605	*1.05*	*0.80*	*1.29*	*0.76*	*1.23*	*1.61*
Prestudy psychosocial, % (n)	11.6 (39)	16.2 (6)	10.0 (6)	9.8 (5)	χ^{23} = 1.08	.782	*0.72*	*1.16*	*1.18*	*1.62*	*1.65*	*1.02*
Prestudy school services, % (n)	51.6 (173)	43.2 (16)	45.0 (27)	43.1 (22)	χ^{23} = 2.50	.476	*1.19*	*1.15*	*1.20*	*0.96*	*1.00*	*1.04*
Extracurriculars, mean (SD)	1.03 (0.97)	1.03 (0.87)	1.05 (1.03)	1.16 (1.03)	F (3,466) = 0.28	.840	0.00	−0.02	−0.13	−0.02	−0.14	−0.11
Parenting, mean (SD)												
Parental involvement	−0.02 (1.79)	−0.35 (1.74)	−0.04 (1.88)	0.10 (1.54)	F (3,470) = 0.38	.768	0.18	0.01	−0.07	−0.17	−0.28	−0.08
Negative ineffective discipline	0.80 (1.62)	1.45 (1.90)	0.66 (1.56)	0.82 (1.55)	F (3,470) = 1.40	.124	−0.39	0.09	−0.01	0.47	0.37	−0.10
Close friends, mean (SD)	1.73 (0.87)	1.39 (0.99)	1.84 (0.80)	1.86 (0.70)	F (3,469) = 2.62	.050	0.39	−0.13	−0.15	−0.52	−0.57	−0.03

[a]All variables measured at baseline unless otherwise noted. Effect sizes are Cohen *d* standardized mean difference scores for continuous variables; categorical effects are quantified by relative risk statistics, which are denoted in italics.
[b]Biological risk score: low maternal age at birth + smoking during pregnancy + hypertensive during pregnancy + cesarean section + preterm + postnatal smoke exposure.
[c]Psychosocial risk score: 3 or more children in family + both parents without college degree + single parent.
[d]Statistically significant after applying false discovery rate correction within outcome domain.
[e]See Supplementary Table 2 for effect sizes for multinomial categorical outcomes.
Abbreviations: BDI = Beck Depression Inventory, CPT = continuous performance test, CD = conduct disorder, CDI = Children's Depression Inventory, Dx = diagnosis, ES = effect size, M = mean, MASC = Multidimensional Anxiety Scale for Children, ODD = oppositional defiant disorder, SCID = Structured Clinical Interview for *DSM*, SNAP = Swanson, Nolan, and Pelham Rating Scale.

Relation Between Environmental Demands and ADHD Remission Status Within the Fluctuating Group

After statistically adjusting for age (see Table 3), significant between-

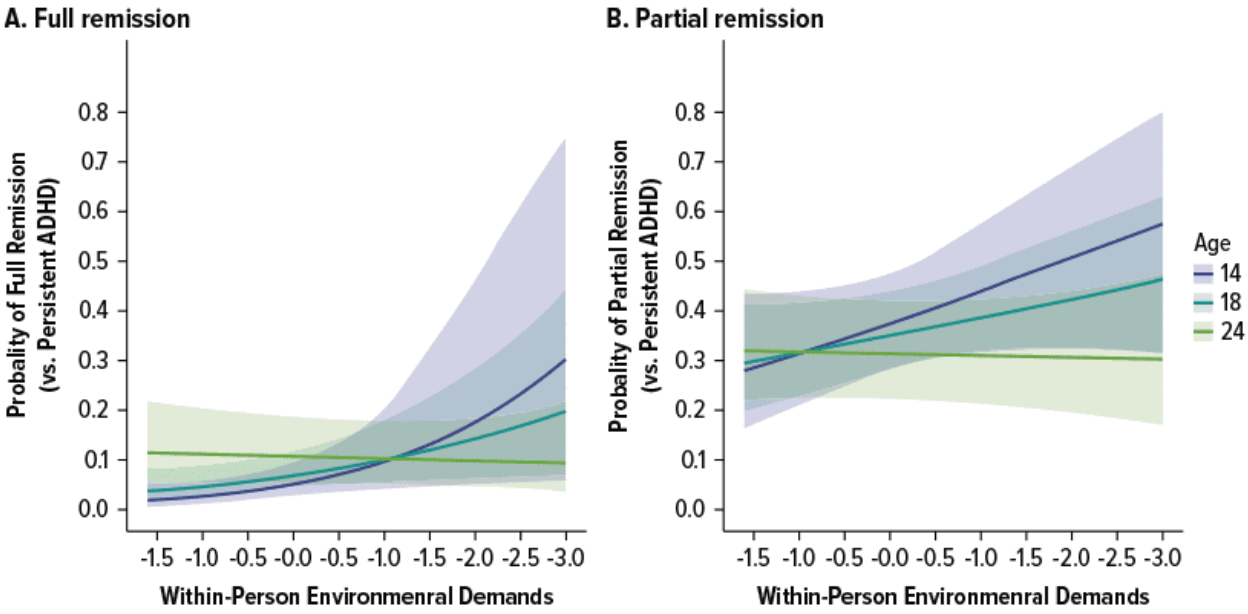
a 1.36 higher odds of experiencing a partial remission period than a persistent period. For the full remission vs persistent comparison, there was also a significant within-person effect of environmental demands, indicating that for each point higher an individual scored at any given time point, compared to their own average level of environmental demands, they were 1.28 times more likely to be experiencing an episode of full remission vs an episode of persistence at that time point. A significant interaction between age and within-person environmental demands indicated that the increased odds of full remission that was associated with higher environmental demands was stronger at younger ages than at older ages (see Figure 2). Specifically, as individuals progressed through adulthood, the within-person associations between environmental demands and remission status were less closely related. There was not a significant within-person effect of environmental demands or a significant interaction between within-person environmental demands and age on the likelihood of experiencing a partial remission vs persistent period. Sensitivity analyses (see Supplementary Table 3) indicated that the between-person associations between environmental demands and remission status were not significant in a model including comorbidity as a covariate.

	Persistence vs full remission				Persistence vs partial remission			
	b	SE	P[a]	OR	b	SE	P[a]	OR
Age[b]	0.08	0.02	**<.001**	1.09	−0.03	0.02	.111	0.97
Demands: between-person	0.46	0.18	**.011**[c]	1.58	0.31	0.13	**.016**[c]	1.36
Demands: within-person	0.25	0.12	**.044**	1.28	0.10	0.08	.198	1.10
Demands: within-person × age	−0.08	0.04	**.041**[c]	0.928	−0.03	0.02	.172	0.97

[a]Statistically significant *P* values noted in boldface.
[b]Grand mean-centered age was included as a covariate.
[c]Result was no longer significant in sensitivity analysis that included comorbidity in the model.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, b = unstandardized beta, OR = odds ratio, SE = standard error.

Figure 2.

Probability of Remission as a Function of Within-Person Environmental Demands and Age[a]



[a]Within-person environmental demands variable is centered at 0 such that a score of 3 on the x-axis represents 3 points above one's person-centered mean level of average demands across included time points.

DISCUSSION

This research validates fluctuating ADHD and details its typical clinical characteristics including: 3 to 4 fluctuations over 16 years, 6- to 7-symptom differences between IN and H/I peaks and troughs, first remission periods in early adolescence, and greater stability in

or protective factors (at least for those diagnosed as ADHD, combined type, in childhood). Among fluctuators, periods of remission (particularly full remission) were associated with *higher* environmental demands, particularly at younger ages.

This research confirms prominent instability within the fluctuating group, rebuffs criticisms that fluctuating ADHD is simply an artifact of categorizing a dimensional trait,[5] and reveals an artifact within endpoint classification of ADHD persistence (ie, similar proportions of fluctuators were temporarily persisters vs remitters at MTA endpoint). ADHD's fluctuating nature does not redesignate it as a state-like disorder with transitory episodes (eg, mood disorders). Other polygenic, chronic, trait-like disorders (eg, autism, personality, and schizophrenia) are also known to fluctuate.[7]

The high prevalence and moderate severity of fluctuating ADHD indicates that it may be the standard clinical course of ADHD—not a rare variant. Stable persistence appears to be a less common variant of ADHD (10.8% of sample) characterized by early and lasting risk for comorbid mood problems, elevated substance use, stable impairments, and low medication utilization relative to severity. The recovery (9.1%) and stable partial remission subgroups (15.6%) may be rare variants marked by milder ADHD and protective factors such as low parental psychopathology or elevated comorbid anxiety (see Table 1 and Table 2). Future work should compare common and rarer ADHD courses on both genetic and time-varying environmental factors. Stable partial remission is particularly intriguing given its positive association with anxiety comorbidity and psychosocial treatment utilization relative to other groups. Although longitudinal course was associated with response to childhood treatment and

well-known bidirectional influences between treatment and ADHD severity in observational designs.[30] Future work must disentangle complex relations between past and ongoing treatment and ADHD fluctuations.

Similar to other MTA investigations, we found protective and deleterious roles of internalizing symptoms as well as relations between ADHD persistence and parental psychopathology.[10,41,42] These variables warrant continued study and may be important to screen for clinically. Contrary to MTA research on endpoint persistence, we did not find relations with baseline ADHD severity and longitudinal ADHD course.[10] Thus, ADHD prognosis may need to reflect a holistic view of the child's life beyond just symptom level during a single assessment.

Periods of remission were associated with higher between- and within-person environmental demands. Though fluctuations in demands and remission appear to coincide (particularly at younger ages), it remains unclear whether remission promotes entry into more demanding environments or greater demands facilitate symptom/impairment management. Perhaps there is a U-shaped demands-remission curve, bidirectional demands-remission relations, or individual differences in the directionality between these variables. The MTA data may be among the best available to investigate fluctuating ADHD; however, our environmental demands variable is an imperfect index measured at 2-year intervals. Data limitations prevented modeling of finer-grained, more complex statistical relations; nonetheless, establishing concurrent fluctuation of ADHD and environmental context is a critical green light for further exploration. Interestingly, higher within-person demands no longer temporally coincided with remission by the mid 20s (see Figure 2), suggesting a more complex influence of

scenario, an individual may have been classified as being partially remitted (rather than persistent) as a function of their low level of demands.

Although the MTA was representative of US demographics at study initiation, it includes fewer girls relative to boys and fewer participants with minoritized ethnic or racial identities relative to white identities, which may limit generalizability. Our multilevel models focused on concurrent fluctuation of remission and demands; future work might investigate timing of remission/recurrence (see Supplementary Appendix 5). Future work might also disentangle the relative contributions of demands levels to ADHD symptom vs impairment levels. Despite the clinical relevance of ADHD fluctuations to late-identified ADHD, long-term symptom monitoring, and expectations for return to care, variations in a trait over time (ie, regression to the mean and homeostatic processes) may be less prognostic than mean trait level. Though we previously documented that informant switching accounts for minimal variance in fluctuations,[5] changes in how informants perceive an individual, rather than true behavioral differences, may explain some fluctuations. Clinicians also wrestle with this challenge.

CONCLUSIONS

ADHD fluctuations are common and substantive. This investigation shows that, when temporarily remitted, individuals with fluctuating ADHD can successfully manage increased responsibilities. Much remains unknown about fluctuating ADHD. Future research should investigate treatment optimization based on longitudinal course of ADHD, building datasets with finer-grained, prospective measurement of environmental and endogenous factors hypothesized as relevant to

that ADHD often fluctuates over time and patient monitoring of symptoms is imperative to trigger as-needed return to care. Clinicians also should partner and collaborate with individuals with ADHD and their families to leverage person-specific environmental factors that appear to positively influence functioning.

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Supplementary Material: Available at Psychiatrist.com.

Clinical Points

- Recent studies suggest that attention-deficit/hyperactivity disorder (ADHD) may commonly fluctuate, but predictors of people who fluctuate and periods of fluctuation remain unclear.
- Long-term monitoring of patient ADHD symptoms and impairments is indicated to adjust treatment according to exacerbations and abatements.

References (42)

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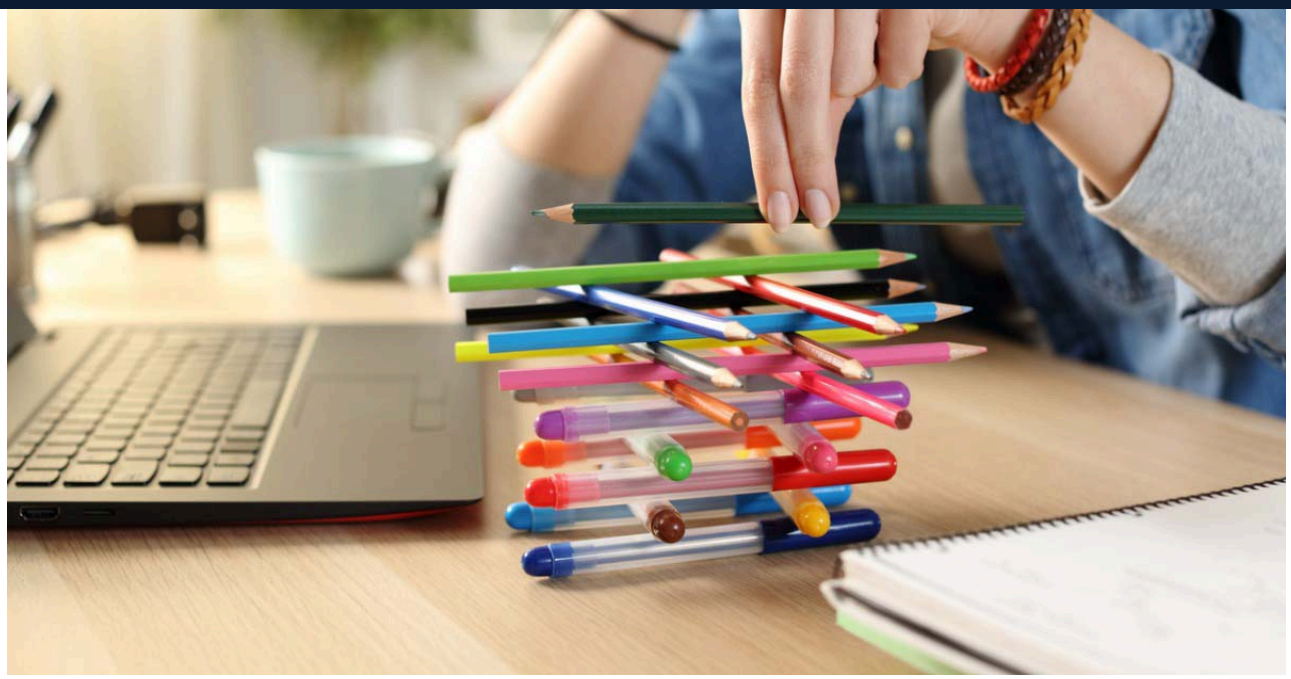

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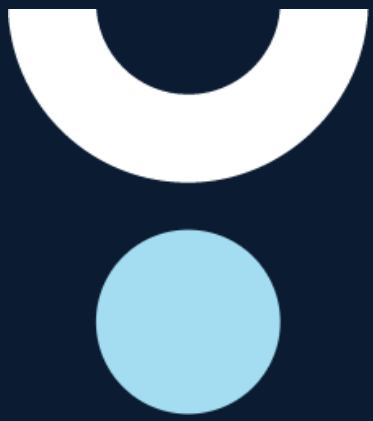

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