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Pubertal stage, sex and behaviour in neurodevelopmental disorders versus typical development: a cross-sectional study

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ABSTRACT

Objective To determine the association between pubertal stage, sex and behavioural profile across and within neurodevelopmental disorders (NDDs) compared with typically developing (TD) youth.

Methods This was a cross-sectional study from the Province of Ontario Neurodevelopmental Disorders network, including children/youth with various NDDs and TD controls. Caregivers completed the Child Behavior Checklist (CBCL). Participants were grouped into three puberty stages: prepuberty (Tanner stage 1), early puberty (Tanner stages 2–3) and late puberty (Tanner stages 4–5). The association between pubertal stage and CBCL scores was assessed controlling for sex and diagnosis.

Results The analysis included 1043 participants (male=733; 70.3%). A three-way interaction between pubertal status, sex and diagnosis was not significant for internalising or externalising behaviour. Diagnosis was significantly associated with CBCL scores for both internalising (p<0.0001) and externalising (p<0.0001) behaviours, with lower scores for TD children than for NDD groups. Late pubertal females showed higher levels of internalising behaviour compared with prepubertal females (p=0.001); males showed no differences. Early pubertal males showed lower levels of externalising behaviour compared with prepubertal males (p=0.01); early pubertal females trended towards higher levels compared with prepubertal females (p=0.051).

Conclusions Internalising/externalising patterns of behaviours across pubertal stages did not differ based on diagnosis. Pubertal females are at higher risk for internalising behaviours.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Existing studies of behaviour and puberty in neurodevelopmental disorders have focused on small groups of children/youth within specific diagnoses and have not included typically developing controls.

WHAT THIS STUDY ADDS

⇒ Children/youth with neurodevelopmental disorders show similar patterns of behaviour levels across stages of puberty compared with typically developing controls; however, they have consistently higher levels of internalising and externalising behaviours across all stages compared with their typically developing peers. In both the neurodevelopmental and typically developing groups, females showed higher internalising behaviour (eg, anxiety, low mood) in pubertal stages compared with prepubertal stages.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Clinicians should be aware of the potential for worsening mental health symptoms during puberty, particularly for females.

INTRODUCTION

Parents and clinicians perceive puberty as a time of worsening mental health and behaviour, particularly in children and youth with neurodevelopmental disorders (NDDs).[1 2] Surprisingly, this belief is based on little evidence. Such information is critically important to provide anticipatory guidance to adolescents with NDDs and their families and to assist clinicians in assessment and management of mood and behaviour issues during puberty.

Puberty is a period associated with biological, social and behavioural changes.[3] It is also a sensitive period for organisation in the brain with the potential for long-lasting effects on brain function and behaviour.[4] Bodily appearance, cognition and behavioural systems mature at different rates and are influenced by both shared and independent stimuli; disruptions in coordination of these developing systems can lead to vulnerability due to mismatch of motivation/arousal and the capacity to regulate thoughts, emotions and behaviours.[5] These individual changes occur in a social milieu, which itself affects and is affected by individual pubertal processes in

a complex relationship between neurodevelopment, puberty and the social environment.[6]

Youth with NDDs, such as autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD), may be at additional risk for mental health issues and interfering behaviour during puberty.[3 7] Sex differences exist in each of these disorders,[8–10] indicating a possible contributory role of exposure to sex steroids early in development[11 12] and raising the possibility that hormone exposure during puberty might lead to further neurodevelopmental differences. In addition, research has shown that children across NDDs exhibit social difficulties.[13] The relationship between social development and neurodevelopment during puberty suggests further vulnerability for children with NDDs during this period that can have lasting impacts on neuronal organisation.

Despite this increased vulnerability, few studies have evaluated the association between puberty and mental health/behaviour in youth with NDDs, particularly compared with typically developing (TD) groups. Case series in ASD have suggested that peripubertal behavioural deterioration may occur in up to one-third of youth.[7 14 15] There is retrospective evidence that early puberty (as reported by university-aged females with ADHD) is associated with increased ADHD symptomatology,[16] though there is no report of symptoms through the duration of puberty. The onset of OCD in women has been linked to reproductive cycle events, including 13% of women reporting onset of OCD in the year after menarche.[17]

These reports suggest potential vulnerability in children and youth with NDDs during puberty that extends beyond emotional and behavioural changes typically experienced during this time.[18] Unfortunately, all work to date has focused within specific diagnoses, limiting our ability to understand shared vulnerability during puberty across NDDs. Importantly, this information can refine guidance provided to families of adolescents with NDDs. The objective of this study was to evaluate the relationship between stage of puberty and internalising/externalising behaviour within and across various NDDs, accounting for sex differences.

METHODS

Setting and participants

This was a cross-sectional study using data collected through the Ontario Brain Institute Province of Ontario Neurodevelopmental Disorders (OBI-POND) network. OBI-POND is a research collaboration across five Ontario centres (Holland Bloorview Kids Rehabilitation Hospital, Toronto; the Hospital for Sick Children, Toronto; McMaster Children's Hospital, Hamilton; Lawson Health Research Institute, London; and Queen's University, Kingston). OBI-POND enrols children with NDDs, including ASD, ADHD, OCD, as well as TD controls, at any time after their diagnosis until age 21 years, 11 months. All caregivers provided informed consent for enrolment in OBI-POND (participants who were capable provided informed consent for their participation). Participants for this analysis were enrolled between February 2012 and March 2019. Participants who completed both the Child Behavior Checklist (CBCL) and the Tanner staging form at the time of enrolment were included.

Participants with a primary diagnosis of ASD, ADHD and OCD were included in the analysis, along with TD controls. Diagnostic assessments were performed on all OBI-POND participants to confirm their reported clinical diagnosis. These included the Autism Diagnostic Observation Schedule[19] and the Autism Diagnostic Interview-Revised[20] for participants with ASD; the Schedule for Affective Disorders and Schizophrenia, Childhood Version (K-SADS)[21] and the Parent Interview for Child Symptoms[22] for participants with ADHD; and the K-SADS and the Children's Yale-Brown Obsessive-Compulsive Scale for Children[23] for participants with OCD. Participants with subthreshold diagnoses were excluded.

Measures

As part of OBI-POND, all participants had caregivers complete the CBCL.[24] The CBCL is a reliable and validated behavioural questionnaire that has been used in many observational studies.[25] CBCL T-scores for internalising and externalising behaviours were used as the dependent variables in the analyses. These are norm referenced for a general population sample in the same age range and sex with an expected mean of 50 across all ages; as such, any effects of puberty would be above and beyond those expected based on age and sex.

Participants aged 8 years or older (or their caregivers when research staff/caregivers felt that participants were not able) completed a Tanner staging form (also called sexual maturity rating), where penile/breast stages of growth (SOG) and pubic hair (PH) development are both reported compared with reference drawings on a scale of 1 (prepubertal) to 5 (postpubertal).[26] Drawings used for self-assessment in a Hong Kong sample showed substantial agreement for SOG and PH for females, with males having substantial agreement for PH and moderate agreement for SOG.[27] SOG and PH ratings were combined into one categorical variable representing pubertal status. Where SOG and PH scores differed by 1, the lower score was used. When scores differed by 2, the intermediate score was used. For participants who had only reported one of PH or SOG, that stage was used as their overall Tanner rating. Tanner ratings were then recorded as prepuberty (stage 1), early puberty (stages 2–3) and late puberty (stages 4–5).

Pubertal staging and the CBCL were completed by 1066 participants. To ensure these measures were contemporaneous, 17 participants with a gap of 6 months or longer between the two measures were excluded. Six participants reported a difference of more than two stages between PH and SOG and were excluded due to concerns about reliability of reporting.

Sex and primary neurodevelopmental diagnosis were included as additional covariables in the model. Information on gender was available for <10% of our sample (77 participants) because it was not collected as part of OBI-POND until 2019. For this reason, gender was not included in the analysis.

Analysis

Statistical analyses were completed using SAS V.9.4 (2002–2012, SAS Institute). Descriptive statistics were used to characterise the sample. To determine if differences in internalising and externalising behaviours across pubertal stage varied by sex and diagnosis, we tested a three-way interaction in an analysis of variance model that allowed for heterogeneous variance across sex, pubertal stage and diagnosis. After removing the non-significant three-way interaction, we assessed whether behaviours across pubertal stage varied by diagnosis across males and females simultaneously by testing the pubertal stage by diagnosis two-way interaction. After dropping both the non-significant pubertal stage by diagnosis two-way interaction and the non-significant sex by diagnosis two-way interaction, we report the differences in behaviours across pubertal stages for males and females separately across all diagnoses.

Patient and public involvement

POND has a Participant Advisory Committee (families and stakeholders from NDD community groups) and a Youth Advisory Committee comprising youth with NDDs.

RESULTS

The analysis included 1043 participants. Demographic information for the sample is summarised in table 1. For both males (X^2=33.1, df=6, p<0.001) and females (X^2=22, df=6, p=0.001), there were significant differences in the distribution across pubertal stages, with more prepubertal representation in the ADHD group. The proportion of males and females by diagnostic category differed significantly (X^2=52.4, df=3, p<0.001), with ASD and ADHD showing an expected higher proportion of males. The informant (ie, person completing the pubertal staging) also differed between the groups, with proportionately higher self-report in the TD group compared with the NDD groups (X^2=93, df=6, p<0.001).

Internalising behaviour

Results for the final internalising behaviour model are presented in table 2 and figure 1. Scores in the TD group were lower than the ASD, ADHD and OCD groups. The three-way interaction between pubertal stage, sex and diagnosis was not significant (F=1.28, df=6, p=0.26; see online supplemental table 1 for full model results). There was a significant interaction between sex and pubertal stage (F=3.55, df=2, p=0.03). Across diagnoses, males showed no significant differences in levels of internalising behaviours based on stage of puberty. Late pubertal females had CBCL scores that were higher by 4.4 points (95% CI −1.4 to 3.8, p=0.001) compared with prepubertal females. This pattern significantly differed (p=0.01) from the pattern in males (difference between prepuberty and late puberty=0.2, 95% CI −1.8 to 2.0, p=0.8).

Externalising behaviour

Results for the final externalising behaviour model are presented in table 3 and figure 2. Here again, scores for the TD group were lower than for the ASD, ADHD and OCD groups. The three-way interaction between pubertal stage, sex and diagnosis was not significant (F=0.59, df=6, p=0.74; online supplemental table 1). There was a significant interaction between sex and pubertal stage (F=6.57, df=2, p=0.002). Early pubertal males showed lower levels of externalising behaviour compared with prepubertal males (difference −2.2, 95% CI −4.0 to −0.5, p=0.01). By contrast, females showed a non-significant trend towards higher levels of externalising behaviour in early puberty versus those in prepuberty (difference 2.8, 95% CI 0 to 5.7, p=0.051). The difference in these patterns between males and females was significant (p=0.003). While both males and females showed lower levels of externalising behaviours in late puberty compared with early puberty, these differences are not statistically significant, although clinically important effects cannot be ruled out (95% CI for males −3.6 to 0.3 and 95% CI for females −4.0 to 1.4).

DISCUSSION

This study examined the association between pubertal stage and behavioural profile across various NDDs. Our analysis is strengthened by the presence of a TD control group. The pattern of behaviours across pubertal stages was similar between the TD group and the NDD groups. A key distinction, however, is that the CBCL scores for the TD groups were consistently lower than for the NDD groups. Hence, although the pattern is similar, families might experience puberty as affecting children with NDDs more than their TD peers.

Across NDD and TD groups, levels of internalising behaviours were the same for males across the different pubertal stages, although the TD group had much lower scores. Across diagnoses, females in late puberty showed higher levels of internalising behaviour compared with their prepubertal counterparts, a pattern which differed significantly from their male peers. Our results echo findings in the general population that have shown increases in anxiety[28] and depression[29] over the adolescent years that are greater for females compared with males. In NDD populations, Gotham *et al*[30] measured internalising behaviours longitudinally in adolescent groups with ASD and with developmental delays and found that increases in internalising behaviours with age were greater for females compared with males. Pubertal stage was not measured in their analysis. Overall, these findings endorse heightened surveillance for internalising behaviours in females with pubertal onset.

Table 1 Sample characteristics

	Typically developing		ASD		ADHD		OCD	
	Male	Female	Male	Female	Male	Female	Male	Female
n	78	53	351	100	226	79	78	78
Race/ethnicity, n (% of non-missing)								
Arab	1 (1)	0	2 (1)	1 (1)	4 (3)	1 (2)	2 (4)	0
Black	3 (4)	1 (2)	16 (7)	1 (1)	4 (3)	6 (10)	0	2 (5)
Chinese	7 (9)	4 (8)	7 (3)	4 (6)	6 (4)	2 (3)	1 (2)	1 (3)
East Asian	1 (1)	0	1 (<1)	0	0	0	2 (4)	0
Indigenous	1 (1)	0	14 (6)	4 (6)	5 (3)	5 (8)	1 (2)	0
Japanese	2 (3)	1 (2)	1 (<1)	0	0	0	0	0
Jewish	1 (1)	1 (2)	10 (4)	3 (4)	19 (13)	8 (13)	1 (2)	1 (3)
Korean	0	1 (2)	0	1 (1)	0	0	2 (4)	0
American/Hispanic	5 (6)	0	11 (5)	0	7 (5)	1 (2)	0	2 (5)
South Asian	4 (5)	3 (6)	5 (2)	2 (3)	4 (3)	2 (3)	5 (11)	0
Southeast Asian	0	1 (2)	2 (1)	2 (3)	0	1 (2)	0	0
West Asian	0	0	2 (1)	0	4 (3)	1 (2)	3 (6)	0
White	60 (77)	47 (89)	195 (83)	57 (83)	116 (78)	51 (84)	42 (89)	34 (89)
Missing ethnicity	0	0	115 (33)	31 (31)	77 (34)	18 (23)	31 (40)	40 (51)
Informant, n (%)								
Missing	4 (5)	3 (6)	16 (5)	7 (7)	15 (7)	3 (4)	4 (5)	2 (3)
Parent	25 (32)	21 (40)	269 (77)	70 (70)	165 (73)	59 (75)	56 (72)	53 (68)
Self	49 (63)	29 (55)	66 (19)	23 (23)	46 (20)	17 (22)	18 (23)	23 (29)
Mean (SD)								
Age	12.4 (2.7)	12.9 (3.2)	12.4 (2.9)	12.6 (3.0)	11.0 (2.5)	10.8 (2.4)	12.6 (2.6)	13.5 (2.5)
Prepuberty	9.7 (1.3)	9.7 (1.2)	10.1 (1.4)	9.8 (1.2)	9.9 (1.5)	9.4 (0.9)	10.5 (1.5)	10.4 (1.5)
Early puberty	12.7 (1.6)	12.7 (1.3)	12.6 (2.0)	11.5 (1.9)	12.3 (1.7)	11.3 (1.1)	12.9 (2.0)	13.0 (2.0)
Late puberty	15.3 (1.8)	16.1 (2.4)	15.8 (1.8)	15.1 (2.5)	15.6 (1.6)	14.5 (2.6)	15.7 (1.3)	15.3 (1.3)
CBCL externalising	42.7 (8.9)	42.5 (7.8)	56.5 (10.6)	57.1 (8.9)	61.0 (10.7)	61.0 (10.6)	49.6 (10.9)	53.5 (10.7)
Prepuberty	45.2 (9.7)	39.7 (7.3)	58.8 (10.9)	56.6 (10.2)	61.6 (10.7)	59.4 (10.1)	51.5 (13.3)	54.3 (5.8)
Early puberty	41.9 (9.4)	43.9 (8.7)	55.7 (9.9)	56.9 (9.6)	61.7 (10.0)	63.5 (10.8)	48.1 (10.0)	55.4 (11.0)
Late puberty	41.0 (6.7)	43.9 (7.4)	54.6 (10.3)	57.6 (7.8)	56.4 (12.0)	59.8 (11.0)	49.2 (8.6)	52.0 (11.9)
CBCL internalising	47.2 (9.0)	47.3 (9.3)	62.5 (9.4)	62.6 (9.6)	61.0 (10.3)	60.3 (11.4)	63.5 (10.9)	63.7 (10.0)
Prepuberty	48.5 (9.0)	44.7 (8.2)	62.6 (9.7)	57.9 (10.5)	60.4 (10.6)	58.1 (10.4)	63.5 (10.4)	64.1 (7.5)
Early puberty	47.8 (9.7)	45.2 (8.9)	62.0 (9.3)	62.3 (7.3)	61.6 (10.0)	62.2 (12.1)	64.0 (8.9)	64.4 (8.0)
Late puberty	45.1 (7.9)	51.2 (10.5)	63.0 (9.3)	65.3 (9.5)	62.5 (9.4)	59.8 (11.4)	62.8 (10.9)	63.0 (12.1)

Child-level ethnicity data were not collected from study inception, leading to a high level of missing data. More than one ethnicity could be reported, meaning percentages will not sum to 100%. Prepuberty: Tanner stage 1. Early puberty: Tanner stages 2–3. Late puberty: Tanner stages 4–5. CBCL scores represent T-scores.
ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CBCL, Child Behavior Checklist; OCD, obsessive-compulsive disorder.

Our data showed lower levels of externalising behaviours in early pubertal males compared with prepubertal males. This difference in levels was significantly different from the pattern in females, which showed a trend (non-significant) towards increased externalising behaviours. Patterns for externalising behaviours during adolescence are mixed in the existing literature. One large Dutch cross-sectional study in a general population of youth found an increasing prevalence of externalising behaviours with each successive Tanner staging in both males and females.[31] An older UK-based study of levels of aggression in a TD population of participants found that males started with higher levels of self-reported aggression, but by late puberty there were no differences between males and females.[32] Verbal aggression against adults increased over the adolescent years; however, this increase was more pronounced among girls. The literature is somewhat sparser when considering NDD

Table 2 Multivariable linear regression* CBCL internalising behaviour predicted scores and score differences

	Puberty stages			Puberty stage differences		
	Prepuberty	Early puberty	Late puberty	Pre to early	Early to late	Pre to late
Males						
TD	47.2 (45.3, 49.1)	47.4 (45.4, 49.3)	47.4 (45.4, 49.5)	0.1 (–1.5, 1.8)	0.1 (–1.8, 2.0)	0.2 (–1.6, 2.0)
ASD	62.4 (61.1, 63.7)	62.5 (61.1, 63.9)	62.6 (61.1, 64.1)			
ADHD	61.0 (59.5, 62.4)	61.1 (59.5, 62.7)	61.2 (59.3, 63.0)			
OCD	63.3 (61.3, 65.2)	63.4 (61.4, 65.4)	63.5 (61.4, 65.6)			
Females						
TD	44.5 (42.1, 46.9)	47.7 (45.3, 50.1)	48.9 (46.7, 51.2)	3.2 (0.4, 6.0) P=0.025	1.2 (–1.4, 3.8)	4.4 (1.7, 7.1) P=0.001
ASD	59.7 (57.5, 61.9)	62.9 (60.8, 65.0)	64.1 (62.2, 66.0)			
ADHD	58.2 (56.0, 60.5)	61.5 (59.2, 63.7)	62.7 (60.5, 64.8)			
OCD	60.6 (58.1, 63.1)	63.8 (61.4, 66.1)	65.0 (62.9, 67.1)			
				Males versus females		
				–3.1 (–6.3, 0.2)	–1.1 (–4.4, 2.1)	–4.2 (–7.4, –1.0) P=0.010

Prepuberty: Tanner stage 1. Early puberty: Tanner stages 2–3. Late puberty: Tanner stages 4–5.
*Pubertal stage (F(2,1034)=4.1, p=0.02). Sex (F(1,1034)=0.2, p=0.7). Diagnosis (F(3,1034)=100.7, p<0.0001). Sex × pubertal stage (F(2,1034)=3.6, p=0.03).
ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CBCL, Child Behavior Checklist; OCD, obsessive-compulsive disorder; TD, typically developing.

groups. A Swiss study of adolescents with ADHD reported decreasing aggression across the adolescent years but did not separate males and females.[33] A longitudinal study of children/youth with ASD showed general patterns of decreasing hyperactivity, and to a lesser extent, irritability, across the adolescent years but again did not distinguish by sex. Our results suggest that, similar to internalising behaviours, females might be at higher risk for externalising behaviours during adolescence. More work is needed to determine the nature of these behaviours in NDD groups, such as increased verbal aggression as suggested by studies of adolescents in the general population.

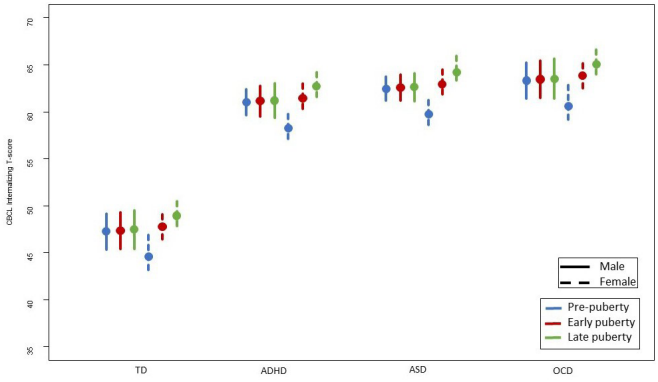

Figure 1 Child Behavior Checklist (CBCL) internalising scores by pubertal stage, sex and diagnosis. ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; OCD, obsessive-compulsive disorder; TD, typically developing.

There are important limitations to our analysis. The data were cross-sectional and did not capture individual behavioural trajectories throughout puberty. We were unable to distinguish between puberty-related effects and age-related effects; to mitigate this limitation, we used CBCL T-scores in order to capture pubertal effects beyond those expected based on age. This analysis did not include whether puberty occurred early or late, both of which have been linked to depressive symptoms in late adolescence.[34] Longitudinal studies measuring pubertal stage and behaviour are needed to optimally disentangle the effects of age and puberty, and should include factors such as IQ and communication skills. Caregivers provided the majority of pubertal staging, which may not be reliable, particularly for children/youth with lower support needs. Both self-report and caregiver report of Tanner staging have been shown to have good reliability in TD females,[35] though self-report in males is less accurate,[36] particularly for SOG.[27] Reports of Tanner staging were chosen over clinician examination to minimise the intrusiveness of participation, allowing for a larger sample size, similar to other studies.[31] We did not have access to information about gender for the vast majority of our sample. Future attention should be paid to the ways in which gender, particularly non-cisgender, interacts with puberty in NDDs. Finally, Tanner staging is a proxy for the internal hormonal states that are thought to influence behaviour[37 38]; fluctuations in hormonal states are not perfectly represented by external appearance.

Table 3 Multivariable linear regression* CBCL externalising behaviour predicted scores and score differences

	Puberty stages			Puberty stage differences		
	Prepuberty	Early puberty	Late puberty	Pre to early	Early to late	Pre to late
Males						
TD	44.2 (42.4, 46.0)	42.0 (40.1, 43.8)	40.3 (38.3, 42.3)	−2.2 (−4.0, −0.5) P=0.010	−1.7 (−3.6, 0.3)	−3.9 (−5.8, −2.0) P<0.0001
ASD	58.3 (57.0, 59.7)	56.1 (54.6, 57.5)	54.4 (52.9, 56.0)			
ADHD	62.2 (60.7, 63.6)	59.9 (58.3, 61.6)	58.3 (56.4, 60.2)			
OCD	52.9 (50.8, 55.0)	50.7 (48.6, 52.8)	49.0 (46.8, 51.2)			
Females						
TD	41.8 (39.5, 44.1)	44.6 (42.3, 47.0)	43.3 (41.2, 45.5)	2.8 (0.0, 5.7)	−1.3 (−4.0, 1.4)	1.5 (−1.2, 4.3)
ASD	55.9 (53.7, 58.2)	58.8 (56.6, 61.0)	57.5 (55.5, 59.4)			
ADHD	59.8 (57.5, 62.0)	62.6 (60.3, 64.9)	61.3 (59.1, 63.5)			
OCD	50.5 (47.9, 53.1)	53.3 (50.9, 55.8)	52.0 (49.8, 54.3)			
				Males versus females		
				−5.1 (−8.4, −1.8) P=0.003	−0.4 (−3.7, 2.9)	−5.4 (−8.7, −2.2) P=0.001

Prepuberty: Tanner stage 1. Early puberty: Tanner stages 2–3. Late puberty: Tanner stages 4–5.
*Pubertal stage ($F(2,1034)=1.7$, p=0.2). Sex ($F(1,1034)=2.44$, p=0.1). Diagnosis ($F(3,1034)=129$, p<0.0001). Sex x pubertal stage ($F(2,1034)=6.6$, p=0.002).
ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CBCL, Child Behavior Checklist; OCD, obsessive-compulsive disorder; TD, typically developing.

In conclusion, our analysis failed to find unique patterns of internalising and externalising behaviours in children/youth with NDDs compared with TD peers. Children with NDDs had higher levels of behaviours compared with TD peers, which might accentuate caregiver perceptions of behaviour changes during the pubertal period. Important sex differences emerged, with females showing significantly higher levels of internalising behaviour at later pubertal stages. Puberty represents an important milestone for adolescents both with and without NDDs, and as such an important opportunity for anticipatory guidance. Our results suggest that females, particularly those with NDDs, should be monitored for affective disorders. Further study is needed on the associations between puberty, sex and externalising behaviours in NDD populations. In the future, longitudinal cohort designs will allow for optimal study of the effects of puberty and behaviours in NDD populations.

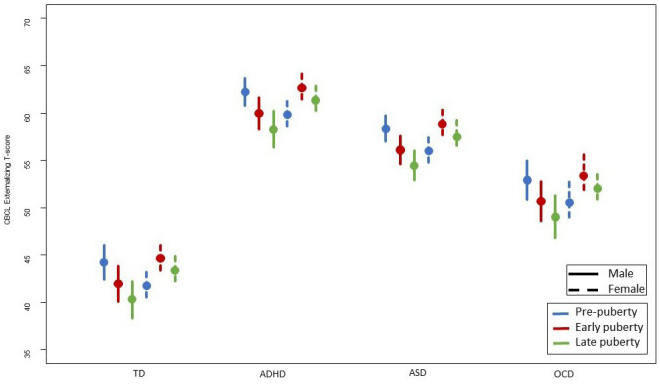

Figure 2 Child Behavior Checklist (CBCL) externalising scores by pubertal stage, sex and diagnosis. ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; OCD, obsessive-compulsive disorder; TD, typically developing.

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Contributors MP developed the research question, codeveloped the methods of data analysis, interpreted the findings, wrote the initial manuscript and approved the submitted manuscript. AD codeveloped the methods of data analysis, performed the data analysis, interpreted the data and findings, and edited and approved the submitted manuscript. MP accepts full responsibility for the finished work and the conduct of the study, had access to the data, and controlled the decision to publish. PA, MA, JC, SG, EK, RN and RS assisted with recruitment and data collection, interpreted the data, and edited and approved the submitted manuscript. EA oversaw the OBI-POND network, provided consultation for the research question and data analysis methods, interpreted the data, and edited and approved the submitted manuscript.

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Competing interests MP has consulted with Addis & Associates/Roche and with the Government of Nova Scotia. RS has served as a consultant to Ehave (cognitive rehabilitation software for ADHD) and Highland Therapeutics and is a

shareholder with Ehave. EA has served as a consultant to Roche and Quadrant. She has received grant funding from Sanofi Canada and SynapDx, Roche; holds a provisional patent for the device 'Anxiety Meter'; receives royalties from American Psychiatric Association Publishing and Springer and editorial honoraria from Wiley; and also the associate editor for Molecular Autism. PA receives grant funding from Biohaven Pharmaceuticals.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Holland Bloorview Kids Rehabilitation Hospital, Toronto (11-280); The Hospital for Sick Children, Toronto (1000012230); McMaster Children's Hospital, Hamilton (12-050); Lawson Health Research Institute, London (103326); and Queen's University, Kingston (6005107). Informed consent was provided by all capable participants and by caregivers for participants who were not capable of providing consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. Participant data used in this study are currently stored in the Brain-CODE Neuroinformatics Platform (https://www.braincode.ca/) managed by the Ontario Brain Institute. Requests to access these data sets should be directed to the Ontario Brain Institute at info@braininstitute.ca.

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