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

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Pubertal stage, sex, and behavior 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 behavioral profile across and within neurodevelopmental disorders (NDDs) compared to 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 pubertal stages: pre-pubertal (Tanner 1), early puberty (Tanner 2-3), and late puberty (Tanner 4-5). The association between pubertal stage and CBCL scores was assessed controlling for sex and diagnosis.

Results: The analysis included 1,043 participants (male=733; 70.3%). A three-way interaction between pubertal status, sex, and diagnosis was not significant for internalizing or externalizing behavior. Diagnosis was significantly associated with CBCL scores for both internalizing *(p*<0.0001) and externalizing *(p*<0.0001) behavior, with lower scores for TD children than for NDD groups. Late pubertal females showed higher levels of internalizing behavior compared to pre-puberty females (*p*=0.001); males showed no differences. Early pubertal males showed lower levels of externalizing behavior compared to pre-puberty (*p*=0.01); early puberty females trended toward higher levels compared to pre-puberty females *(p*=0.051).

Conclusions: Internalizing/externalizing patterns of behaviors across pubertal stages did not differ based on diagnosis. Pubertal females are at higher risk for internalizing behaviors.

Keywords: Puberty, Behavior, Developmental disorders

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Key Messages:

What is already known on this topic:

Existing studies of behavior 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 behavior levels across stages of puberty compared to typically developing controls; however, they have consistently higher levels of internalizing and externalizing behavior across all stages compared to their typically developing peers. In both the neurodevelopmental and typically developing groups, females showed higher internalizing behavior (e.g. anxiety, low mood) in pubertal stages compared to pre-pubertal 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.

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Parents and clinicians perceive puberty as a time of worsening mental health and behavior, particularly in children and youth with neurodevelopmental disorders (NDD).[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 behavior issues during puberty.

Puberty is a period associated with biological, social, and behavioral changes.[3] It is also a sensitive period for organization in the brain with the potential for long-lasting effects on brain function and behaviour.[4] Bodily appearance, cognition, and behavioral 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 behaviors.[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 organization.

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Despite this increased vulnerability, relatively few studies have evaluated the association between puberty and mental health/behaviour in youth with NDDs, particularly compared to typically developing (TD) groups. Case series in ASD have suggested that peri-pubertal behavioral 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 internalizing/externalizing behavior 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 centers (redacted names). OBI-POND enrols children with NDDs, including ASD, ADHD, OCD, as well as typically developing (TD)

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controls, at any time after their diagnosis until age 21 years, 11 months. All caregivers provided informed consent for enrollment 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 enrollment 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 sub-threshold diagnoses were excluded.

Measures

As part of OBI-POND, all participants had caregivers complete the Child Behavior Checklist (CBCL).[24] The CBCL is a reliable and validated behavioral questionnaire that has been used in many observational studies.[25] CBCL T-scores for internalizing and externalizing behavior 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.

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Participants aged eight 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; SMR), where penile/breast stages of growth (SOG) and pubic hair (PH) development are both reported compared to reference drawings on a scale of one (pre-pubertal) to five (post-pubertal).[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 pre-pubertal (stage 1), early pubertal (stages 2-3), and late pubertal (stage 4-5).

Pubertal staging and the CBCL were completed by 1066 participants. To ensure these measures were contemporaneous, 17 participants with a gap of six 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

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Statistical analyses were completed using SAS 9.4 (2002-2012, SAS Institute Inc., Cary, NC, USA). Descriptive statistics were used to characterize the sample. To determine if differences in internalizing and externalizing behaviors across pubertal stage varied by sex and diagnosis, we tested a 3-way interaction in an ANOVA model that allowed for heterogeneous variance across sex, pubertal stage, and diagnosis. After removing the non-significant 3-way interaction, we assessed whether behaviors across pubertal stage varied by diagnosis across males and females simultaneously by testing the pubertal stage by diagnosis 2-way interaction. After dropping both the non-significant pubertal stage by diagnosis 2-way interaction and the non-significant sex by diagnosis 2-way interaction, we report the differences in behaviors across pubertal stages for males and females separately, across all diagnoses.

Ethics approval:

This project received research ethics approval from 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. Informed consent was provided by all capable participants and by caregivers for participants who were not capable of providing consent.

Patient and Public Involvement:

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

Results:

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The analysis included 1043 participants. Demographic information for the sample is summarized in **Table 1**. For both males (X^2 = 33.1, degrees of freedom [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 pre-pubertal 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 (i.e., person completing the pubertal staging) also differed between the groups, with proportionately higher self-report in the TD group compared to the NDD groups (X^2 = 93, *df* 6, *p* < 0.001).

Internalizing behavior

Results for the internalizing behavior 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). 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 internalizing behaviors based on stage of puberty. Late pubertal females had CBCL scores that were higher by 4.4 points (95% confidence interval [CI] -1.4, 3.8; p=0.001) compared to pre-pubertal females. This pattern significantly differed (p=0.01) from the pattern in males (difference between pre- and late puberty = 0.2; 95% CI -1.8, 2.0; p=0.8).

Externalizing behavior

Results for the externalizing behavior 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

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interaction between pubertal stage, sex, and diagnosis was not significant ($F = 0.59$, df 6, p = 0.74). 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 externalizing behavior compared to pre-pubertal males (difference -2.2, 95% CI -4.0, -0.5; p=0.01). By contrast, females showed a non-significant trend toward higher levels of externalizing behavior in early puberty versus those in pre-puberty (difference 2.8, 95% CI 0, 5.7, p=0.051). The difference in these patterns between males and females was significant (p=0.003). While both males and females show lower levels of externalizing behaviors 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 -3.6,0.3 and 95%CL for females -4.0 to 1.4).

Discussion:

This study examined the association between pubertal stage and behavioral profile across various NDDs. Our analysis is strengthened by the presence of a TD control group. Our results show that the pattern of behaviors 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, it is likely that families experience puberty as affecting children with NDDs more than their TD peers.

Across NDD and TD groups, levels of internalizing behaviors 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 internalizing behavior compared to their pre-pubertal counterparts, a pattern which differed significantly from their male peers. Our

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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 to males. In NDD populations, Gotham, Brunwasser and Lord[30] measured internalizing behaviors longitudinally in adolescent groups with ASD and with developmental delays and found that increases in internalizing behaviors with age were greater for females compared to males. Pubertal stage was not measured in their analysis. Overall, these findings endorse heightened surveillance for internalizing behaviors in females with pubertal onset.

Our data showed lower levels of externalizing behaviors in early pubertal males compared to pre-pubertal males. This difference in levels was significantly different from the pattern in females, which showed a trend (non-significant) toward increased externalizing behaviors. Patterns for externalizing behaviors 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 externalizing behaviors with each successive Tanner stage in both males and females.[31] An older UK-based study of levels of aggression in a typically developing 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 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 internalizing behaviors, females might be at higher risk for externalizing behaviors during adolescence. More

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work is needed to determine the nature of these behaviors in NDD groups, such as increased verbal aggression as suggested by studies of adolescents in the general population.

There are important limitations to our analysis. The data were cross-sectional and did not capture individual behavioral 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 behavior 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 stage have been shown to have good reliability in typically developing 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 minimize 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 behavior;[37,38] fluctuations in hormonal states are not perfectly represented by external appearance.

In conclusion, our analysis failed to find unique patterns of internalizing and externalizing behavior in children/youth with NDDs compared to TD peers. Children with NDDs had higher levels of behaviors compared to TD peers, which might accentuate caregiver

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perceptions of behavior changes during the pubertal period. Important sex differences emerged, with females showing significantly higher levels of internalizing behavior 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 externalizing behaviors in NDD populations. In the future, longitudinal cohort designs will allow for optimal study of the effects of puberty and behaviors in NDD populations.

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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)
Pre puberty	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 Externalizing	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)
Pre puberty	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 Internalizing	47.2 (9.0)	47.3 (9.3)	62.5 (9.4)	62.6 (9.6)	61.0 (10.3)	60.3 (11.4)	61.5 (10.9)	63.7 (10.0)
Pre puberty	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)

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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)	63.8 (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%. Pre-puberty: 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; sd: standard deviation

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Table 2: Multivariable linear regression[1] CBCL internalizing behavior predicted scores and score differences

	Puberty stages			Puberty stage differences		
	Pre-puberty	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* = .025	1.2 (-1.4, 3.8)	4.4 (1.7, 7.1) *p* = .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 vs. Females		
				-3.1 (-6.3, 0.2)	-1.1 (-4.4, 2.1)	-4.2 (-7.4, -1.0) *p* = .010

[1] Pubertal stage ($F(2,1034) = 4.1$, $p = .02$); Sex ($F(1,1034) = 0.2$, $p = 0.7$); Diagnosis ($F(3,1034) = 100.7$, $p < .0001$); Sex x Pubertal stage ($F(2,1034) = 3.6$, $p = .03$)

Pre-puberty: Tanner stage 1; Early puberty: Tanner stages 2-3; Late puberty: Tanner stages 4-5. ADHD: attention-deficit/hyperactivity disorder; ASD: autism spectrum disorder; CBCL: Child Behavior Checklist; OCD: obsessive compulsive disorder; TD: typically developing

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Table 3: Multivariable linear regression[1] CBCL externalizing behavior predicted scores and score differences

	Puberty stages			Puberty stage differences		
	Pre-puberty	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)			
ASD	58.3 (57.0, 59.7)	56.1 (54.6, 57.5)	54.4 (52.9, 56.0)	-2.2 (-4.0, -0.5)	-1.7 (-3.6, 0.2)	-3.9 (-5.8, -2.0)
ADHD	62.2 (60.7, 63.6)	59.9 (58.3, 61.6)	58.3 (56.4, 60.2)	*p* = .010		*p* < .0001
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)			
ASD	55.9 (53.7, 58.2)	58.8 (56.6, 61.0)	57.5 (55.5, 59.4)	2.8 (0.0, 5.7)	-1.3 (-4.0, 1.4)	1.5 (-1.2, 4.3)
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 vs. Females		
				-5.1 (-8.4, -1.8)	-0.4 (-3.7, 2.9)	-5.4 (-8.7, -2.2)
				p = .003		*p* = .001

[1] Pubertal stage ($F(2,1034)$ = 1.7, p = .2); Sex ($F(1,1034)$ = 2.44, p = 0.1); Diagnosis ($F(3,1034)$ = 129, p < .0001); Sex x Pubertal stage ($F(2,1034)$ = 6.6, p = .002)

Pre-puberty: Tanner stage 1; Early puberty: Tanner stages 2-3; Late puberty: Tanner stages 4-5. ADHD: attention-deficit/hyperactivity disorder; ASD: autism spectrum disorder; CBCL: Child Behavior Checklist; OCD: obsessive compulsive disorder; TD: typically developing

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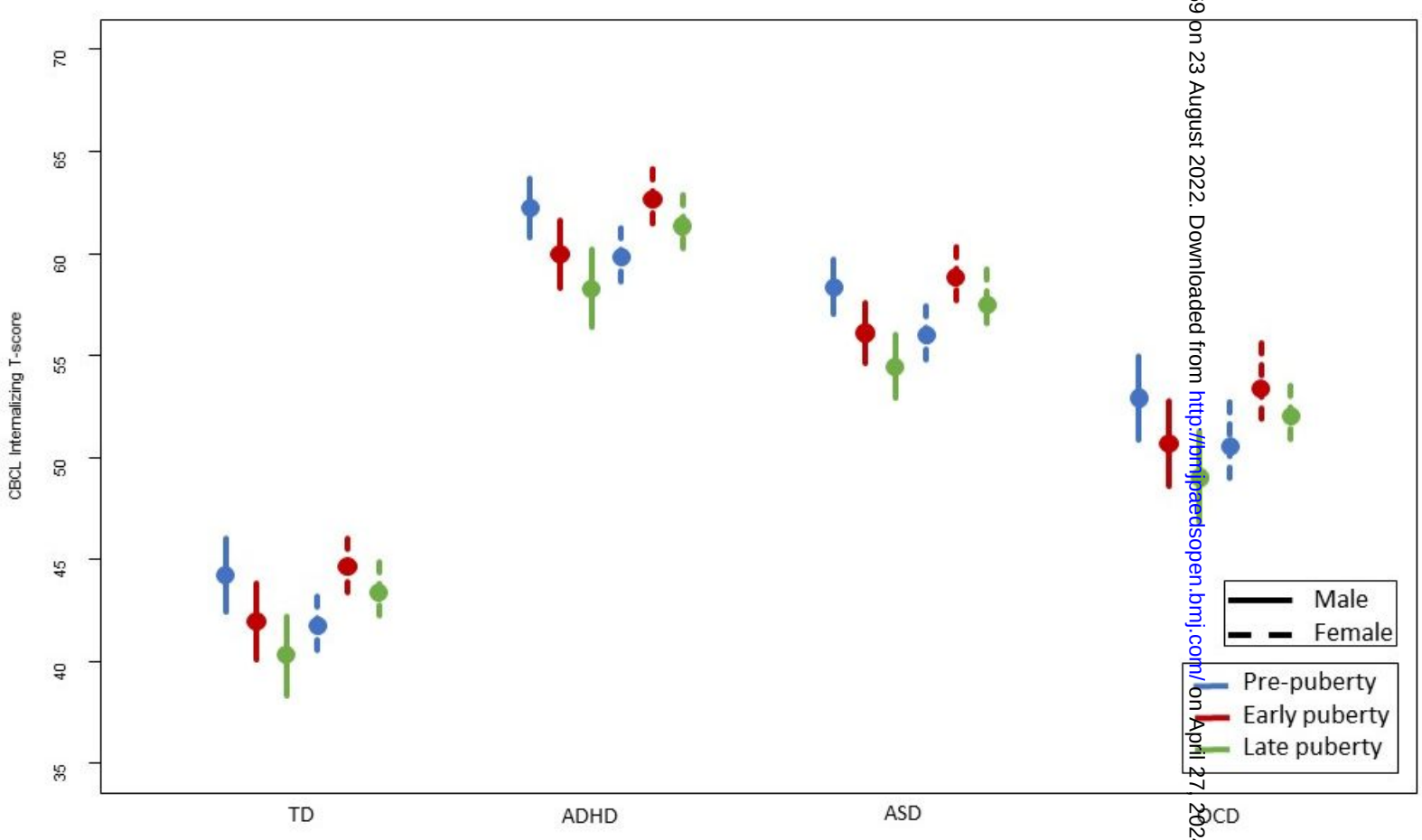

Figure 1: CBCL Internalizing scores by pubertal stage, sex, and diagnosis. ADHD: attention-deficit/hyperactivity disorder; ASD: autism spectrum disorder; OCD: obsessive compulsive disorder; TD: typical development.

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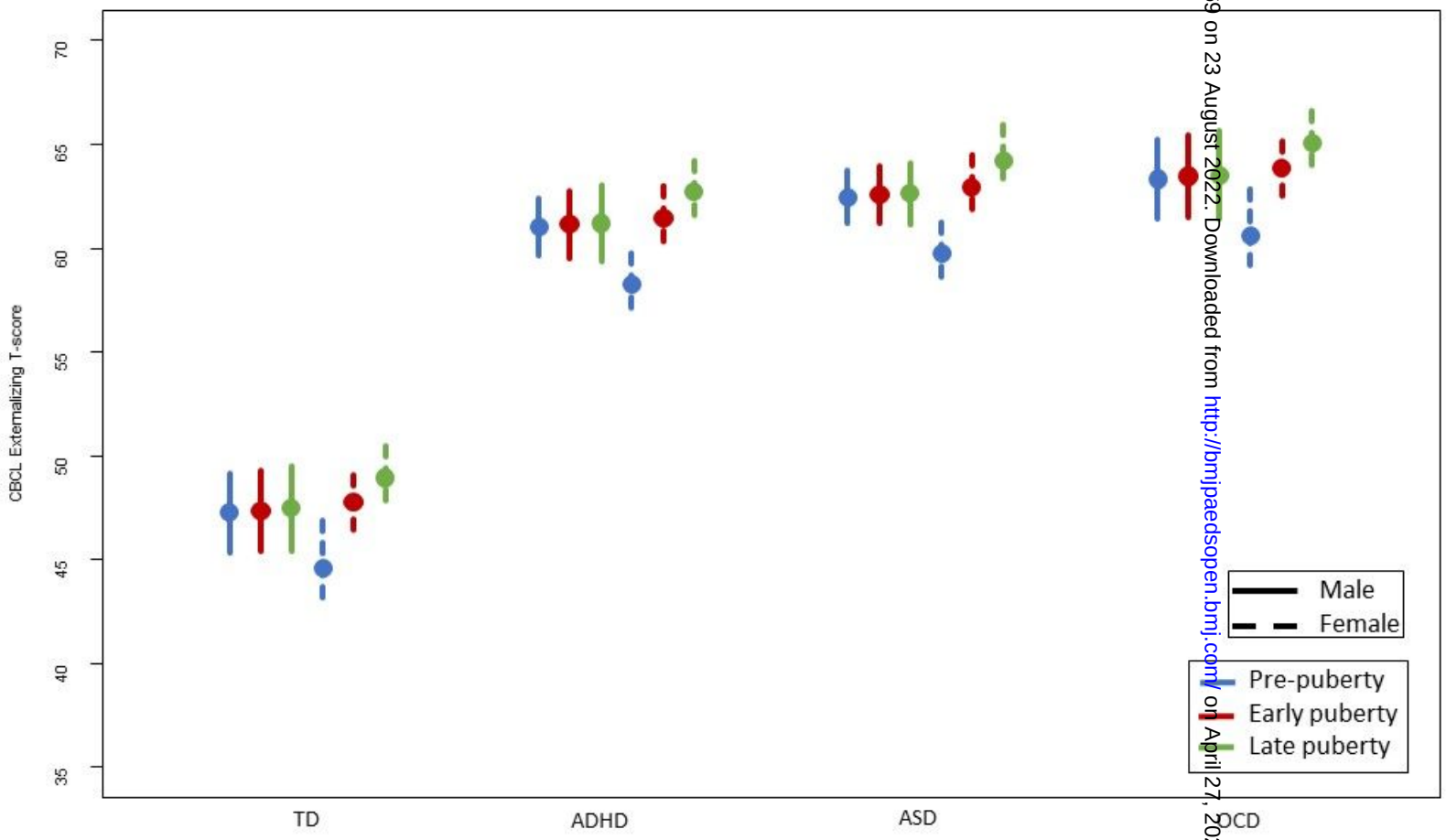

Figure 2: CBCL Externalizing scores by pubertal stage, sex, and diagnosis. ADHD: attention-deficit/hyperactivity disorder; ASD: autism spectrum disorder; OCD: obsessive compulsive disorder; TD: typical development.

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

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Pubertal stage, sex, and behavior 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 behavioral profile across and within neurodevelopmental disorders (NDDs) compared to 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 pubertal stages: pre-pubertal (Tanner 1), early puberty (Tanner 2-3), and late puberty (Tanner 4-5). The association between pubertal stage and CBCL scores was assessed controlling for sex and diagnosis.

Results: The analysis included 1,043 participants (male=733; 70.3%). A three-way interaction between pubertal status, sex, and diagnosis was not significant for internalizing or externalizing behavior. Diagnosis was significantly associated with CBCL scores for both internalizing *(p*<0.0001) and externalizing *(p*<0.0001) behavior, with lower scores for TD children than for NDD groups. Late pubertal females showed higher levels of internalizing behavior compared to pre-puberty females (*p*=0.001); males showed no differences. Early pubertal males showed lower levels of externalizing behavior compared to pre-puberty (*p*=0.01); early puberty females trended toward higher levels compared to pre-puberty females *(p*=0.051).

Conclusions: Internalizing/externalizing patterns of behaviors across pubertal stages did not differ based on diagnosis. Pubertal females are at higher risk for internalizing behaviors.

Keywords: Puberty, Behavior, Developmental disorders

Key Messages:

What is already known on this topic:

Existing studies of behavior 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 behavior levels across stages of puberty compared to typically developing controls; however, they have consistently higher levels of internalizing and externalizing behavior across all stages compared to their typically developing peers. In both the neurodevelopmental and typically developing groups, females showed higher internalizing behavior (e.g. anxiety, low mood) in pubertal stages compared to pre-pubertal 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.

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Parents and clinicians perceive puberty as a time of worsening mental health and behavior, 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 behavior issues during puberty.

Puberty is a period associated with biological, social, and behavioral changes.[3] It is also a sensitive period for organization in the brain with the potential for long-lasting effects on brain function and behaviour.[4] Bodily appearance, cognition, and behavioral 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 behaviors.[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 organization.

Despite this increased vulnerability, few studies have evaluated the association between puberty and mental health/behaviour in youth with NDDs, particularly compared to typically developing (TD) groups. Case series in ASD have suggested that peri-pubertal behavioral 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 internalizing/externalizing behavior 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 centers (redacted names). OBI-POND enrols children with NDDs, including ASD, ADHD, OCD, as well as typically developing (TD)

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controls, at any time after their diagnosis until age 21 years, 11 months. All caregivers provided informed consent for enrollment 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 enrollment 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 sub-threshold diagnoses were excluded.

Measures

As part of OBI-POND, all participants had caregivers complete the Child Behavior Checklist (CBCL).[24] The CBCL is a reliable and validated behavioral questionnaire that has been used in many observational studies.[25] CBCL T-scores for internalizing and externalizing behavior 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 eight 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; SMR), where penile/breast stages of growth (SOG) and pubic hair (PH) development are both reported compared to reference drawings on a scale of one (pre-pubertal) to five (post-pubertal).[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 pre-pubertal (stage 1), early pubertal (stages 2-3), and late pubertal (stage 4-5).

Pubertal staging and the CBCL were completed by 1066 participants. To ensure these measures were contemporaneous, 17 participants with a gap of six 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

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Statistical analyses were completed using SAS 9.4 (2002-2012, SAS Institute Inc., Cary, NC, USA). Descriptive statistics were used to characterize the sample. To determine if differences in internalizing and externalizing behaviors across pubertal stage varied by sex and diagnosis, we tested a 3-way interaction in an ANOVA model that allowed for heterogeneous variance across sex, pubertal stage, and diagnosis. After removing the non-significant 3-way interaction, we assessed whether behaviors across pubertal stage varied by diagnosis across males and females simultaneously by testing the pubertal stage by diagnosis 2-way interaction. After dropping both the non-significant pubertal stage by diagnosis 2-way interaction and the non-significant sex by diagnosis 2-way interaction, we report the differences in behaviors across pubertal stages for males and females separately, across all diagnoses.

Ethics approval:

This project received research ethics approval from 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. Informed consent was provided by all capable participants and by caregivers for participants who were not capable of providing consent.

Patient and Public Involvement:

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

Results:

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The analysis included 1043 participants. Demographic information for the sample is summarized in **Table 1**. For both males (X^2 = 33.1, degrees of freedom [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 pre-pubertal 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 (i.e., person completing the pubertal staging) also differed between the groups, with proportionately higher self-report in the TD group compared to the NDD groups (X^2 = 93, *df* 6, *p* < 0.001).

Internalizing behavior

Results for the final internalizing behavior 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 Supplementary 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 internalizing behaviors based on stage of puberty. Late pubertal females had CBCL scores that were higher by 4.4 points (95% confidence interval [CI] -1.4, 3.8; p=0.001) compared to pre-pubertal females. This pattern significantly differed (p=0.01) from the pattern in males (difference between pre- and late puberty = 0.2; 95% CI -1.8, 2.0; p=0.8).

Externalizing behavior

Results for the final externalizing behavior 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

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three-way interaction between pubertal stage, sex, and diagnosis was not significant ($F = 0.59$, df 6, p = 0.74; Supplementary 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 externalizing behavior compared to pre-pubertal males (difference -2.2, 95% CI -4.0, -0.5; p=0.01). By contrast, females showed a non-significant trend toward higher levels of externalizing behavior in early puberty versus those in pre-puberty (difference 2.8, 95% CI 0, 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 externalizing behaviors 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 -3.6,0.3 and 95%CL for females -4.0 to 1.4).

Discussion:

This study examined the association between pubertal stage and behavioral profile across various NDDs. Our analysis is strengthened by the presence of a TD control group. The pattern of behaviors 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 internalizing behaviors 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 internalizing behavior compared to their pre-pubertal counterparts, a pattern which differed significantly from their male peers. Our

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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 to males. In NDD populations, Gotham, Brunwasser and Lord[30] measured internalizing behaviors longitudinally in adolescent groups with ASD and with developmental delays and found that increases in internalizing behaviors with age were greater for females compared to males. Pubertal stage was not measured in their analysis. Overall, these findings endorse heightened surveillance for internalizing behaviors in females with pubertal onset.

Our data showed lower levels of externalizing behaviors in early pubertal males compared to pre-pubertal males. This difference in levels was significantly different from the pattern in females, which showed a trend (non-significant) toward increased externalizing behaviors. Patterns for externalizing behaviors 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 externalizing behaviors with each successive Tanner stage in both males and females.[31] An older UK-based study of levels of aggression in a typically developing 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 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 internalizing behaviors, females might be at higher risk for externalizing behaviors during adolescence. More

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work is needed to determine the nature of these behaviors in NDD groups, such as increased verbal aggression as suggested by studies of adolescents in the general population.

There are important limitations to our analysis. The data were cross-sectional and did not capture individual behavioral 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 behavior 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 stage have been shown to have good reliability in typically developing 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 minimize 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 behavior;[37,38] fluctuations in hormonal states are not perfectly represented by external appearance.

In conclusion, our analysis failed to find unique patterns of internalizing and externalizing behavior in children/youth with NDDs compared to TD peers. Children with NDDs had higher levels of behaviors compared to TD peers, which might accentuate caregiver

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perceptions of behavior changes during the pubertal period. Important sex differences emerged, with females showing significantly higher levels of internalizing behavior 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 externalizing behaviors in NDD populations. In the future, longitudinal cohort designs will allow for optimal study of the effects of puberty and behaviors in NDD populations.

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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)
Pre puberty	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 Externalizing	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)
Pre puberty	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 Internalizing	47.2 (9.0)	47.3 (9.3)	62.5 (9.4)	62.6 (9.6)	61.0 (10.3)	60.3 (11.4)	61.5 (10.9)	63.7 (10.0)
Pre puberty	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)

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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%. Pre-puberty: 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; sd: standard deviation

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Table 2: Multivariable linear regression[1] CBCL internalizing behavior predicted scores and score differences

	Puberty stages			Puberty stage differences		
	Pre-puberty	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)			
ASD	62.4 (61.1, 63.7)	62.5 (61.1, 63.9)	62.6 (61.1, 64.1)	0.1 (-1.5, 1.8)	0.1 (-1.8, 2.0)	0.2 (-1.6, 2.0)
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)			
ASD	59.7 (57.5, 61.9)	62.9 (60.8, 65.0)	64.1 (62.2, 66.0)	3.2 (0.4, 6.0)	1.2 (-1.4, 3.8)	4.4 (1.7, 7.1)
ADHD	58.2 (56.0, 60.5)	61.5 (59.2, 63.7)	62.7 (60.5, 64.8)	*p* = .025		*p* = .001
OCD	60.6 (58.1, 63.1)	63.8 (61.4, 66.1)	65.0 (62.9, 67.1)			
				Males vs. Females		
				-3.1 (-6.3, 0.2)	-1.1 (-4.4, 2.1)	-4.2 (-7.4, -1.0) *p* = .010

[1] Pubertal stage ($F(2,1034) = 4.1$, $p = .02$); Sex ($F(1,1034) = 0.2$, $p = 0.7$); Diagnosis ($F(3,1034) = 100.7$, $p < .0001$); Sex x Pubertal stage ($F(2,1034) = 3.6$, $p = .03$)

Pre-puberty: Tanner stage 1; Early puberty: Tanner stages 2-3; Late puberty: Tanner stages 4-5. ADHD: attention-deficit/hyperactivity disorder; ASD: autism spectrum disorder; CBCL: Child Behavior Checklist; OCD: obsessive compulsive disorder; TD: typically developing

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Table 3: Multivariable linear regression[1] CBCL externalizing behavior predicted scores and score differences

	Puberty stages			Puberty stage differences		
	Pre-puberty	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)			
ASD	58.3 (57.0, 59.7)	56.1 (54.6, 57.5)	54.4 (52.9, 56.0)	-2.2 (-4.0, -0.5)	-1.7 (-3.6, 0.2)	-3.9 (-5.8, -2.0)
ADHD	62.2 (60.7, 63.6)	59.9 (58.3, 61.6)	58.3 (56.4, 60.2)	*p* = .010		*p* < .0001
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)			
ASD	55.9 (53.7, 58.2)	58.8 (56.6, 61.0)	57.5 (55.5, 59.4)	2.8 (0.0, 5.7)	-1.3 (-4.0, 1.4)	1.5 (-1.2, 4.3)
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 vs. Females		
				-5.1 (-8.4, -1.8)	-0.4 (-3.7, 2.9)	-5.4 (-8.7, -2.2)
				p = .003		*p* = .001

[1] Pubertal stage ($F(2,1034)$ = 1.7, p = .2); Sex ($F(1,1034)$ = 2.44, p = 0.1); Diagnosis ($F(3,1034)$ = 129, p < .0001); Sex x Pubertal stage ($F(2,1034)$ = 6.6, p = .002)

Pre-puberty: Tanner stage 1; Early puberty: Tanner stages 2-3; Late puberty: Tanner stages 4-5. ADHD: attention-deficit/hyperactivity disorder; ASD: autism spectrum disorder; CBCL: Child Behavior Checklist; OCD: obsessive compulsive disorder; TD: typically developing

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Figure Legends:

Figure 1: CBCL Internalizing scores by pubertal stage, sex, and diagnosis. ADHD: attention-deficit/hyperactivity disorder; ASD: autism spectrum disorder; OCD: obsessive compulsive disorder; TD: typical development.

Figure 2: CBCL Externalizing scores by pubertal stage, sex, and diagnosis. ADHD: attention-deficit/hyperactivity disorder; ASD: autism spectrum disorder; OCD: obsessive compulsive disorder; TD: typical development.

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Figure 1

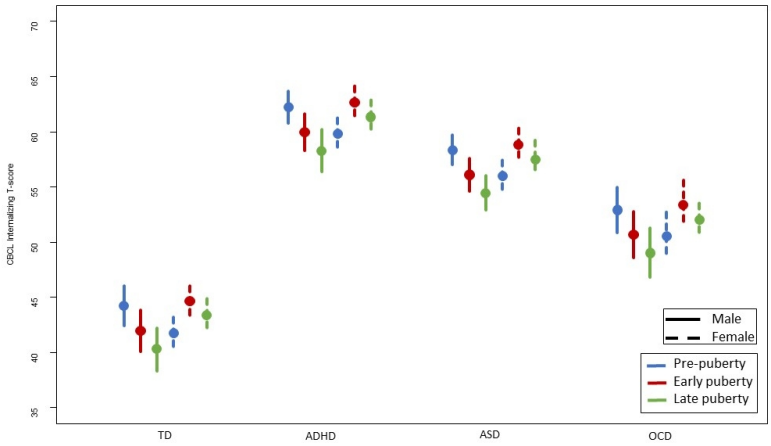

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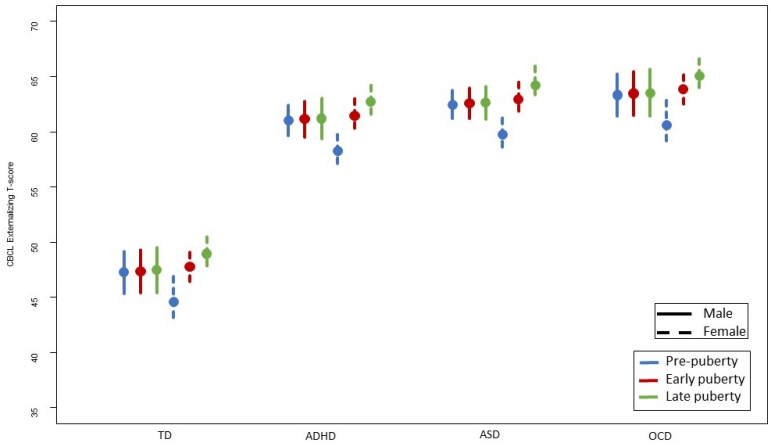
Figure 2



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Supplementary Table 1: CBCL score differences by pubertal stage, diagnosis, and sex

	ADHD	ASD	OCD	TD
Internalizing behavior score difference: pre-puberty vs early puberty				
Males	5.1 (-0.4, 10.7)	4.4 (-0.5, 9.3)	0.3 (-4.7, 5.3)	0.5 (-5.4, 6.4)
Difference from TD	4.6 (-3.5, 12.7)	3.9 (-3.8, 11.6)	-0.2 (-7.9, 7.5)	
Females	1.2 (-1.8, 4.2)	-0.6 (-3.0, 1.8)	0.5 (-4.5, 5.6)	-0.7 (-5.6, 4.3)
Difference from TD	1.9 (-3.9, 7.7)	0.1 (-5.4, 5.6)	1.2 (-5.9, 8.3)	
Internalizing behavior score difference: early puberty vs late puberty				
Males	-3.4 (-10.6, 3.8)	3.0 (-0.9, 6.8)	-1.5 (-6.4, 3.5)	6.0 (-0.5, 12.4)
Difference from TD	-9.4 (-19.0, 0.3)	-3.0 (-10.5, 4.5)	-7.4 (-15.5, 0.7)	
Females	0.9 (-3.3, 5.0)	1.0 (-1.5, 3.5)	-1.2 (-6.8, 4.4)	-2.7 (-7.4, 2.1)
Difference from TD	3.6 (-2.8, 9.9)	3.6 (-1.8, 9.0)	1.5 (-5.9, 8.9)	
Externalizing behavior score difference: pre-puberty vs early puberty				
Males	4.1 (-1.1, 9.2)	0.4 (-5.0, 5.7)	1.0 (-4.2, 6.3)	4.1 (-1.4, 9.7)
Difference from TD	-0.1 (-7.6, 7.5)	-3.8 (-11.5, 3.9)	-3.1 (-10.7, 4.5)	
Females	0.1 (-2.9, 3.1)	-3.1 (-5.7, -0.5)	-3.5 (-9.6, 2.7)	-3.3 (-8.3, 1.8)
Difference from TD	3.3 (-2.6, 9.2)	0.2 (-5.5, 5.9)	-0.2 (-8.2, 7.8)	
Externalizing behavior score difference: early puberty vs late puberty				
Males	-3.7 (-10.5, 3.1)	0.6 (-3.6, 4.8)	-3.4 (-9.1, 2.4)	0.0 (-5.4, 5.5)
Difference from TD	-3.7 (-12.4, 5.0)	0.6 (-6.3, 7.5)	-3.4 (-11.3, 4.5)	
Females	-5.3 (-10.2, -0.3)	-1.0 (-3.7, 1.7)	1.1 (-4.0, 6.3)	-0.9 (-5.3, 3.5)
Difference from TD	-4.4 (-11.0, 2.3)	-0.1 (-5.3, 5.0)	2.0 (-4.8, 8.8)	

ADHD: attention-deficit hyperactivity disorder; ASD: autism spectrum disorder; CBCL: Child Behavior Checklist; OCD: obsessive compulsive disorder; TD: typically developing.

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Puberty, sex, and behavior in neurodevelopmental disorders versus typical development

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Abstract

Objective: To determine the association between pubertal stage, sex, and behavioral profile across and within neurodevelopmental disorders (NDDs) compared to 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 pubertal stages: pre-pubertal (Tanner 1), early puberty (Tanner 2-3), and late puberty (Tanner 4-5). The association between pubertal stage and CBCL scores was assessed controlling for sex and diagnosis.

Results: The analysis included 1,043 participants (male=733; 70.3%). A three-way interaction between pubertal status, sex, and diagnosis was not significant for internalizing or externalizing behavior. Diagnosis was significantly associated with CBCL scores for both internalizing *(p*<0.0001) and externalizing *(p*<0.0001) behavior, with lower scores for TD children than for NDD groups. Late pubertal females showed higher levels of internalizing behavior compared to pre-puberty females (*p*=0.001); males showed no differences. Early pubertal males showed lower levels of externalizing behavior compared to pre-puberty (*p*=0.01); early puberty females trended toward higher levels compared to pre-puberty females *(p*=0.051).

Conclusions: Internalizing/externalizing patterns of behaviors across pubertal stages did not differ based on diagnosis. Pubertal females are at higher risk for internalizing behaviors.

Keywords: Puberty, Behavior, Developmental disorders

Key Messages:

What is already known on this topic:

Existing studies of behavior 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: Our study looked at a large sample of children/youth with neurodevelopmental disorders, as well as typically developing controls, to examine the association between puberty stage, sex, and behavior. Children/youth with neurodevelopmental disorders show similar patterns of behavior levels across stages of puberty compared to typically developing controls; however, they have consistently higher levels of internalizing and externalizing behavior across all stages compared to their typically developing peers. In both the neurodevelopmental and typically developing groups, females showed higher internalizing behavior (e.g. anxiety, low mood) in pubertal stages compared to pre-pubertal 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.

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Background:

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

Puberty is a period associated with biological, social, and behavioral changes.[3] It is also a sensitive period for organization in the brain with the potential for long-lasting effects on brain function and behaviour.[4] Bodily appearance, cognition, and behavioral systems mature at different rates and are influenced by both shared and independent stimuli; disruptions in coordination of these developing systems can lead to particular vulnerability due to mismatch of motivation/arousal and the capacity to regulate thoughts, emotions, and behaviors.[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

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development and neurodevelopment during puberty suggests further vulnerability for children with NDDs during this period that can have lasting impacts on neuronal organization.

Despite this increased vulnerability, relatively few studies have evaluated the association between puberty and mental health/behaviour in youth with NDDs, particularly compared to typically developing (TD) groups. Case series in ASD have suggested that peri-pubertal behavioral 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, while limited, 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 pubertal guidance provided to families of adolescents with NDDs. The objective of this study was to evaluate the relationship between stage of puberty and internalizing/externalizing behavior 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

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is a research collaboration across five Ontario centers (redacted names). OBI-POND enrols children with NDDs, including ASD, ADHD, OCD, as well as typically developing (TD) controls. All caregivers provided informed consent for enrollment 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. All OBI-POND participants aged eight or older were screened for inclusion in the present analysis. Participants who completed both the Child Behavior Checklist (CBCL) and the Tanner staging form 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 sub-threshold diagnoses were excluded.

Measures

As part of the OBI-POND protocol, all participants had caregivers complete the Child Behavior Checklist (CBCL).[24] The CBCL is a reliable and validated behavioral questionnaire that has been used in many observational studies.[25] CBCL T-scores for internalizing and externalizing behavior 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

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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 eight years or older (or their caregivers when research staff/caregivers felt that participants were not able) completed a Tanner staging form, where penile/breast stages of growth (SOG) and pubic hair (PH) development are both reported compared to reference pictures on a scale of one (pre-pubertal) to five (post-pubertal).[26,27] To ensure that SOG and PH were included, these ratings were combined into one categorical variable representing pubertal status. The mean of the SOG and PH ratings was calculated for each participant, with any scores between whole integers rounded down. 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 pre-pubertal (stage 1), early pubertal (stages 2-3), and late pubertal (stage 4-5).

One thousand and sixty-six participants completed pubertal staging and the CBCL. To ensure that pubertal staging was contemporaneous with the CBCL, 17 participants with a gap of six 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

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Statistical analyses were completed using SAS 9.4 (2002-2012, SAS Institute Inc., Cary, NC, USA). Descriptive statistics were used to characterize the sample. To determine if differences in internalizing and externalizing behaviors across pubertal stage varied by sex and diagnosis, we tested a 3-way interaction in an ANOVA model that allowed for heterogeneous variance across sex, pubertal stage, and diagnosis. After removing the non-significant 3-way interaction, we assessed whether behaviors across pubertal stage varied by diagnosis across males and females simultaneously by testing the pubertal stage by diagnosis 2-way interaction. Finally, after dropping both the non-significant pubertal stage by diagnosis 2-way interaction and the non-significant sex by diagnosis 2-way interaction, we report the differences in behaviors across pubertal stages for males and females separately, across all diagnoses.

Ethics approval:

This project received research ethics approval from 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. Informed consent was provided by all capable participants and by caregivers for participants who were not capable of providing consent.

Patient and Public Involvement:

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

Results:

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One thousand and forty-three participants were included in the analysis. Demographic information for the sample is summarized in **Table 1**. For both males ($X^2 = 33.1$, degrees of freedom [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 pre-pubertal 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 (i.e., person completing the pubertal staging) also differed between the groups, with proportionately higher self-report in the TD group compared to the NDD groups ($X^2 = 93$, *df* 6, $p < 0.001$).

Internalizing behavior

Results for the internalizing behavior model are presented in **Table 2**. 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, $p = 0.26$). 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 internalizing behaviors based on stage of puberty. Late pubertal females had CBCL scores that were higher by 4.4 points (95% confidence interval [CI] -1.4, 3.8; p=0.001) compared to pre-pubertal females. This pattern significantly differed (p=0.01) from the pattern in males (difference between pre- and late puberty = 0.2; 95% CI -1.8, 2.0; p=0.8).

Externalizing behavior

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Results for the externalizing behavior model are presented in **Table 3**. 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). 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 externalizing behavior compared to pre-pubertal males (difference -2.2, 95% CI -4.0, -0.5; p=0.01). By contrast, females showed a non-significant trend toward higher levels of externalizing behavior in early puberty versus those in pre-puberty (difference 2.8, 95% CI 0, 5.7, p=0.051). The difference in these patterns between males and females was significant (p=0.003). While both males and females show lower levels of externalizing behaviors 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 -3.6,0.3 and 95%CL for females -4.0 to 1.4).

Discussion:

To our knowledge, this is the first study to examine the association between pubertal stage and behavioral profile across various NDDs. Our analysis is strengthened by the presence of a TD control group. Our results show that the pattern of behaviors 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. As such, although the pattern is similar, it is likely that families experience puberty as affecting children with NDDs more than their TD peers.

Across NDD and TD groups, the levels of internalizing behaviors were the same for males across the different pubertal stages, although the TD group had much lower scores. Across

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diagnoses, females in late puberty showed higher levels of internalizing behavior compared to their pre-pubertal 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 to males. In NDD populations, Gotham, Brunwasser and Lord[30] measured internalizing behaviors longitudinally in adolescent groups with ASD and with developmental delays and found that increases in internalizing behaviors with age were greater for females compared to males. Pubertal stage was not measured in their analysis. Overall, these findings endorse heightened surveillance for internalizing behaviors in females with pubertal onset.

Our data showed lower levels of externalizing behaviors in early pubertal males compared to pre-pubertal males. This difference in levels was significantly different from the pattern in females, which showed a trend (non-significant) toward increased externalizing behaviors. Patterns for externalizing behaviors 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 externalizing behaviors with each successive Tanner stage in both males and females.[31] An older UK-based study of levels of aggression in a typically developing 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 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

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years but again did not distinguish by sex. Our results suggest that, similar to internalizing behaviors, females might be at higher risk for externalizing behaviors during adolescence. More work is needed to determine the nature of these behaviors in NDD groups, such as increased verbal aggression as suggested by studies of adolescents in the general population.

There are important limitations to our analysis. The data were cross-sectional and did not capture individual behavioral trajectories throughout puberty. We were unable to distinguish between puberty-related effects and age-related effects due to the cross-sectional nature of the study; 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 behavior are needed to optimally disentangle the effects of age and puberty. 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 PH stage have been shown to have good reliability in typically developing females,[35] though self-report in males is less accurate.[36] Reports of Tanner staging were chosen over clinician examination to minimize 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 behavior;[37,38] fluctuations in hormonal states are not perfectly represented by external appearance.

In conclusion, our analysis failed to find unique patterns of internalizing and externalizing behavior in children/youth with NDDs compared to TD peers. Children with NDDs

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had higher levels of behaviors compared to TD peers, which might accentuate caregiver perceptions of behavior changes during the pubertal period. Important sex differences emerged, with females showing significantly higher levels of internalizing behavior at later pubertal stages and a pattern of higher externalizing behaviors with pubertal onset compared to males. 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 externalizing behaviors in NDD populations. In the future, longitudinal cohort designs will allow for optimal study of the effects of puberty and behaviors in NDD populations.

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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)
Pubertal stage, n (%)								
Pre puberty	26 (33)	18 (34)	136 (39)	25 (25)	127 (56)	34 (43)	28 (36)	15 (19)
Puberty	29 (37)	15 (28)	109 (31)	28 (28)	70 (31)	30 (38)	28 (36)	25 (32)
Late puberty	23 (29)	20 (38)	107 (30)	47 (47)	29 (13)	15 (19)	22 (28)	38 (49)
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)
CBCL externalizing	42.7 (8.9)	42.5 (7.8)	56.5 (10.6)	57.1 (8.9)	61.0 (10.7)	61.0 (10.6)	62.6 (10.9)	53.5 (10.7)
CBCL internalizing	47.2 (9.0)	47.3 (9.3)	62.5 (9.4)	62.6 (9.6)	61.0 (10.3)	60.3 (11.4)	62.5 (10.9)	63.7 (10.0)

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%. Pre-puberty: Tanner stage 1; Early puberty: Tanner stages 2-3; Late puberty: Tanner stages

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4-5. ADHD: attention-deficit/hyperactivity disorder; ASD: autism spectrum disorder; CBCL: Child Behavior Checklist; OCD: obsessive compulsive disorder; sd: standard deviation

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Table 2: Multivariable linear regression[1] CBCL internalizing behavior predicted scores and score differences

	Puberty stages			Puberty stage differences		
	Pre-puberty	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* = .025	1.2 (-1.4, 3.8)	4.4 (1.7, 7.1) *p* = .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 vs. Females		
				-3.1 (-6.3, 0.2)	-1.1 (-4.4, 2.2)	-4.2 (-7.4, -1.0) *p* = .010

[1] Pubertal stage ($F(2,1034) = 4.1$, $p = .02$); Sex ($F(1,1034) = 0.2$, $p = 0.7$); Diagnosis ($F(3,1034) = 100.7$, $p < .0001$); Sex x Pubertal stage ($F(2,1034) = 3.6$, $p = .03$)

Pre-puberty: Tanner stage 1; Early puberty: Tanner stages 2-3; Late puberty: Tanner stages 4-5. ADHD: attention-deficit/hyperactivity disorder; ASD: autism spectrum disorder; CBCL: Child Behavior Checklist; OCD: obsessive compulsive disorder; TD: typically developing

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Table 3: Multivariable linear regression[1] CBCL externalizing behavior predicted scores and score differences

	Puberty stages			Puberty stage differences		
	Pre-puberty	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)			
ASD	58.3 (57.0, 59.7)	56.1 (54.6, 57.5)	54.4 (52.9, 56.0)	-2.2 (-4.0, -0.5)	-1.7 (-3.6, 0.2)	-3.9 (-5.8, -2.0)
ADHD	62.2 (60.7, 63.6)	59.9 (58.3, 61.6)	58.3 (56.4, 60.2)	*p* = .010		*p* < .0001
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)			
ASD	55.9 (53.7, 58.2)	58.8 (56.6, 61.0)	57.5 (55.5, 59.4)	2.8 (0.0, 5.7)	-1.3 (-4.0, 1.4)	1.5 (-1.2, 4.3)
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 vs. Females		
				-5.1 (-8.4, -1.8)	-0.4 (-3.7, 2.9)	-5.4 (-8.7, -2.2)
				p = .003		*p* = .001

[1] Pubertal stage ($F(2,1034)$ = 1.7, p = .2); Sex ($F(1,1034)$ = 2.44, p = 0.1); Diagnosis ($F(3,1034)$ = 129, p < .0001); Sex x Pubertal stage ($F(2,1034)$ = 6.6, p = .002)

Pre-puberty: Tanner stage 1; Early puberty: Tanner stages 2-3; Late puberty: Tanner stages 4-5. ADHD: attention-deficit/hyperactivity disorder; ASD: autism spectrum disorder; CBCL: Child Behavior Checklist; OCD: obsessive compulsive disorder; TD: typically developing

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