The Impact of Suppressing Puberty on Neuropsychological Function

Sallie Baxendale[1]

[1]Affiliation not available

January 14, 2024

UCL, Queen Square, Institute of Neurology

Running Title: Puberty blockers and cognitive function

ABSTRACT

Concerns have been raised regarding the neuropsychological impact of medications that interrupt puberty, given the magnitude and complexity of changes that occur in brain function and structure during this sensitive window of neurodevelopment. This review examines the literature on the impact of pubertal suppression on cognitive and behavioural function in animals and humans. In mammals the effects are complex and often sex specific. There is no evidence that cognitive effects are fully reversible following discontinuation of treatment. No human studies have systematically explored the impact of these treatments on neuropsychological function with an adequate baseline and follow up. However there is some evidence of a detrimental impact of pubertal suppression on IQ, concordant with findings in the wider literature on gonadotropin-hormone-releasing-hormone expression in relevant brain structures. Critical questions remain unanswered regarding the nature, extent and permanence of any arrested development of cognitive function that may be associated with pharmacological blocking of puberty in humans. The impact of puberal suppression on measures of neuropsychological functions should be an urgent priority for future research. Neuropsychologists should be an integral member of the multidisciplinary team caring for people treated with puberty blockers to monitor the impact of these treatments.

Keywords: puberty, cognition, neurodevelopment; memory; intelligence; gonadotropin-hormone-releasing-hormone (GnRH); review

Key Points

1. Adolescence is a critical window of neurodevelopment and puberty plays a critical role in these neurodevelopmental processes.

2. The suppression of puberty impacts brain structure and the development of social and cognitive functions in mammals, the effects are complex and often sex specific.

3. No human studies have systematically explored the neuropsychological impact of pubertal suppression in transgender adolescents with an adequate baseline and follow up.

4. Animal studies, single case reports and studies of the impact of puberty blockers in children with precocious puberty indicate that these treatments may be associated with reductions in IQ.

4. The impact of pubertal suppression on measures of neuropsychological functions should be an urgent priority for future research.

Introduction

Puberty blockers and cross sex hormones are prescribed to transgender and gender diverse (TGD) young people with the aim of aligning physical appearance with gender identity, as part of a gender-affirming model of care[1]. The medications most commonly used to suppress puberty are gonadotropin-releasing hormone (GnRH) analogues. The number of young people seeking gender affirming treatments has grown significantly over the past 10 years [2,3]. Data from the Gender Identity Development Service (GIDS) in the UK indicates an over 3,000% increase in referrals to the service over an 8-year period from 2009 to 2016. This increase was most marked in females and adolescent females in particular, where the numbers increased by more than 7,000% over the seven year period.

Given the magnitude and complexity of changes that occur in brain function and structure during puberty [4–8] concerns have been raised regarding the impact of medications that interrupt and interfere with this process during this important period of neurodevelopment [9]. In a statement of expert consensus from 24 international specialists11Specialists in neurodevelopment, gender development, puberty, neuroendocrinology and research methods, the impact of pubertal suppression on different aspects of neuropsychological function comprised the majority of research priorities identified, with 9 of the 17 priorities related to possible neuropsychological impacts, namely: effects on executive function, social awareness, functional connectivity, brain structure/volume, emotional awareness, IQ, risk taking, processing speed and memory[9].

Unsurprisingly, given the critical role of puberty in the development of the brain's anterior regions including the prefrontal cortex[4], the study of executive functions/control and attention topped the list of neuropsychological priorities for future research. The expression of GnRH receptors outside the reproductive axis in brain areas such as the hippocampus and amygdala also highlight learning, memory and emotional processing as relevant areas of neuropsychological interest in outcome studies in these patients[10–12].

The first part of this paper summarises our contemporary understanding of puberty from a neuropsychological perspective as the driver of a sensitive 'window of opportunity' for the development of executive functions and social cognition. A brief overview of our current state of knowledge regarding of the role of pubertal hormones in the functional and structural brain changes that occur during adolescence is presented. This literature provides the medical and scientific rationale for neuropsychological outcomes to be included as an essential component of any evaluation of outcome following pharmacological interventions that suppress or delay puberty in adolescents.

Since the current neuropsychological literature is not sufficient to allow for a more precise systematic review [3], the second part of the manuscript presents a scoping review of the literature that has examined the impact of pubertal suppression on cognitive/neuropsychological function in both animal and human studies. For clarity, in this review trans women/girls are referred to as male-to-female and trans men/boys as female-to-male.

Puberty as a critical window in neurodevelopment

The concept of critical 'windows' of plasticity during neurodevelopment refers to specific periods in infancy, childhood and adolescence when the developing brain is programmed to generate dedicated neuronal networks in response to environmental inputs [13,14]. A period is defined as a 'critical window' if the brain requires a specific input to allow for the optimal development of a particular function (for example, exposure to language or visual stimuli). If the neural network is left without the correct input or stimulation, the functions served by that circuit will be permanently compromised[15]. Essential inputs may be internal, for example hormonal or nutritional state [16] and external, for example presence/absence of environmental stimuli [17]. Neural networks that develop in impoverished environments during sensitive periods can sometimes be remoulded by subsequent experiences in later life, although function may always remain suboptimal[17,18]. Windows of plasticity for neurodevelopment are staggered throughout development (from birth to the third decade of life) and follow a set pattern with sensory pathways (vision, hearing) prioritised in infancy, followed by motor and language functions in early childhood [19,20]. Adolescence is a critical window of development for executive functions (behavioural and cognitive) and social cognition [21].

Adolescence: A Critical Period for Synaptic Pruning & Myelination

The approximate 100 trillion synaptic connections [22]that subserve normal adult function do not develop in a linear fashion. Brain development involves both progressive (proliferation, neurite outgrowth, synapse connectivity) and regressive events (cell death, axon pruning, synapse elimination) [23,24]. The regressive events are just as much an integral part of the brain maturation process as the progressive processes. Approximately half of the neurons formed during brain development do not survive into adulthood, with most eliminated via apoptosis or other forms of programmed cell death in utero or early childhood [25,26]. Just as some cells are programmed to die once they have served their purpose in neurodevelopment, similarly the brain is programmed to eliminate initially over-produced synapses [27], a process known as pruning. During childhood, neurons enthusiastically establish trillions of synaptic connections as the individual learns how the world works and their place and agency within it. Dendritic spine density in childhood is three times greater than that seen in adults prior to puberty [28]. Whilst it was initially thought that synaptic pruning in the cerebral cortex was completed by age 16[29] it is now recognised that substantial pruning continues well beyond adolescence and into the third decade of life before stabilizing at the adult level [28]. However, not all changes in the adolescent brain are regressive. Although myelination begins in utero and continues into adulthood, myelin production escalates significantly during adolescence – with biological sex being a significant determinant, particularly in females [30], resulting in significant increases in both the speed of electrical transmission along axons and the energy efficiency of this process.

Biological sex is not just a significant determinant of myelin distribution. A review of MRI studies of male and female brain structure found that adolescence was a time of divergence in the structural characteristics of the brain. Unsurprisingly, sex differences in structures with a high density of sex steroid receptors such as the caudate nucleus, amygdala, hippocampus, and cerebellum have been reported. These differences are dynamic and change over the course of development during adolescence. Regional cortical gray matter volumes follow an inverted U shaped developmental trajectory with peak size occurring one to three years earlier in females compared to males. Whilst white matter volumes increase throughout adolescence in both sexes, this process occurs more rapidly in adolescent males resulting in an increasing magnitude of sex differences. [31]

The role of puberty vs chronological age in neurodevelopment in adolescence

Hormonal changes in puberty are not just responsible for the development of physical secondary sex characteristics, they also drive many of the neurodevelopmental changes in the adolescent brain described above, particularly with respect to the development of frontal cortical circuits, and hippocampal and amygdala connectivity[7,32–35]. In a functional MRI study of 105, 8–19 year olds, Ravindranath et al. found that whilst chronological age was associated with activations in the right dorsolateral prefrontal cortex on a task requiring inhibitory control, puberty stage was associated with activation in the right ventrolateral prefrontal cortex. Metrics of broader connectivity between the ventrolateral prefrontal cortex and cingulate were also associated with puberty stage. The authors conclude that whilst age-related developmental processes may support maturation of brain systems underlying the ability to inhibit a response, processes associated with puberty may play a larger role in the effectiveness of generating cognitive control responses [33].

In summary, puberty is characterised by both regressive and progressive stages of brain development. Unlike earlier developmental milestones, many of these processes are associated with pubertal stage rather than chronological age [33,36–39] and hormonal regulation plays an important part in these developments. The prefrontal cortex undergoes significant rewiring during puberty, with corresponding behavioural changes in associated executive functions including impulse control, decision making and goal directed behaviours. Other behavioural manifestations of the rewiring process in puberty include enhanced reactivity to social and emotional stimuli, especially in relation to peers, and changes in the evaluation of potential rewards[4,21,40–45]. The male and female brain develops differently during adolescence both in terms of structural connectivity and developmental trajectory. The critical role that puberty plays in the development of these functions indicates that neuropsychological outcomes should be an integral part of any clinical protocol implemented to assess the potential impacts of treatments that suppress this process and that natal sex should be a critical

variable in any examination of this impact.

LITERATURE REVIEW

METHODS:

Search strategy and selection criteria

All studies reporting neuropsychological, neurobehavioral or cognitive impacts of GnRH analogues in pubertal suppression in animals or humans were sought. Searches were conducted on PubMed, Embase, Web of Science and PsycINFO in April 2023 using the following terms: 'GnRH*' or 'Lupron' AND 'Pubert*' and any of the following neuropsychological Terms: Cogniti*, OR Neuropsychol*, OR 'Executive', OR 'Language', OR 'Memory', OR 'Learning', OR 'Spatial', OR 'Intelligence', OR 'IQ', OR 'Processing', OR 'Attention', OR 'Social'. The search was limited to English language publications.

Excluding duplicates, the search strategy returned a total of 646 papers across the four search engines for initial review: See Figure 1 for PRISMA flow diagram.

Review articles, book chapters and conference proceedings were excluded from the review. The remaining abstracts (n=498) were reviewed for reports of any quantitative or qualitative measure of cognitive, neurobehavioral or neuropsychological function assessed or described in relation to the administration of GnRH analogues for puberty suppression in either clinical or experimental settings. Forty two records met these criteria and the full text was reviewed. Citation searching in these publications revealed a further possible 10 citations for review.

RESULTS

A number of relevant studies have been presented at conferences but have not subsequently been published in peer reviewed journal articles, for example (Embree et al., 2013; J. Godfrey et al., 2012; Haraldsen, 2011). Sixteen peer reviewed studies that have examined the impact of suppressing puberty with GnHR analogues on cognitive, neurobehavioural or neuropsychological function were identified with the search strategy described. The majority of these studies (n=11) have been conducted in animals.

Animal Studies

The wider search strategy identified experimental studies on the physiological impacts of GnRHa in 17 species of animals (including hyenas, sheep, goats, rats, naked mole rats, giant pouched rats, mice, hamsters, macaques, rhesus monkeys, marmoset monkeys, carp, gilt, chicken, pigs, cows and dogs). Eleven of these studies reported the impact of pharmacological puberty suppression on indices of behavioural function in the animal. These studies are summarised in Table 2. The majority of these studies (n=8) have been conducted in the same flock of sheep using twin controls [10,11,46–51]. Two studies in monkeys [52,53] and one mouse study [54]were also identified. Measures of brain structure were reported in 5 studies and included structural MRI, resting state functional MRI and histopathology (see Table 1).

The behavioural and cognitive measures used in these animal studies can be broadly divided into three categories;

1. Positive interactions with the environment (e.g. locomotion, food acquisition, preferences for novel objects, hyponeophagia, social preferences)

2. Responses to stress (responses to social isolation, vocalisations, emotional reactivity, forced swim test, human intruder test, manifestations of social status)

3. Performance on cognitive tasks (maze tasks).

As can be seen in Table 1, the results from these studies indicate that treatment with GnRHa has a detrimental impact on learning and the development of social behaviours and responses to stress in mammals[10,11,46–48,50,51,53,54]. Sex-specific effects were observed in multiple studies [11,49,54]. In male sheep, impairments in spatial memory associated with the treatment were not fully reversed following discontinuation of treatment[51]. Significant effects of treatment were also evident on measures of brain structure including overall volume[53], functional connectivity [52] and neuronal density [54].

The results from these studies are broadly consistent and indicate that the suppression of puberty impacts brain structure and the development of social and cognitive functions in mammals, but the impacts are complex and often sex specific, consistent with the MRI evidence of sex specific differences in neurodevelopment in human adolescence[31]. There is no evidence in the animal literature that these effects are reversible following discontinuation of treatment.

Human Studies

The search strategy identified just 5 studies that have reported some aspect of neuropsychological function following the administration of medications to suppress puberty young people. Two studies reported the impact of treatment with GnHR a in young people with precocious puberty (CPP) and three reported neuropsychological test performance in people treated for gender dysphoria. One of these studies was a single case study.

Central Precocious Puberty

In the only human study that established a baseline prior to treatment, Mul et al (2001) examined the response to treatment with GnRH analogues on a number of psychosocial outcomes including the Child Behaviour Checklist and performance on the shortened version of the Wechsler Intelligence Scales for Children in a group of 25 girls treated with GnRHa for early puberty. Three years after treatment commenced, the group as a whole had experienced a loss in both performance IQ and full scale IQ, with a decline of 7 points in the latter. Whilst statistically significant at $p<0.01$, the authors state that the decrease in IQ was not 'clinically relevant', a conclusion repeated in a later citation of the study [55]. Whilst the average loss of IQ points was 7, it is noteworthy that at least one patient in this study experienced a significant loss of 15 points or more, since the highest IQ score in the group was 138 at baseline and this dropped to 123 following treatment.

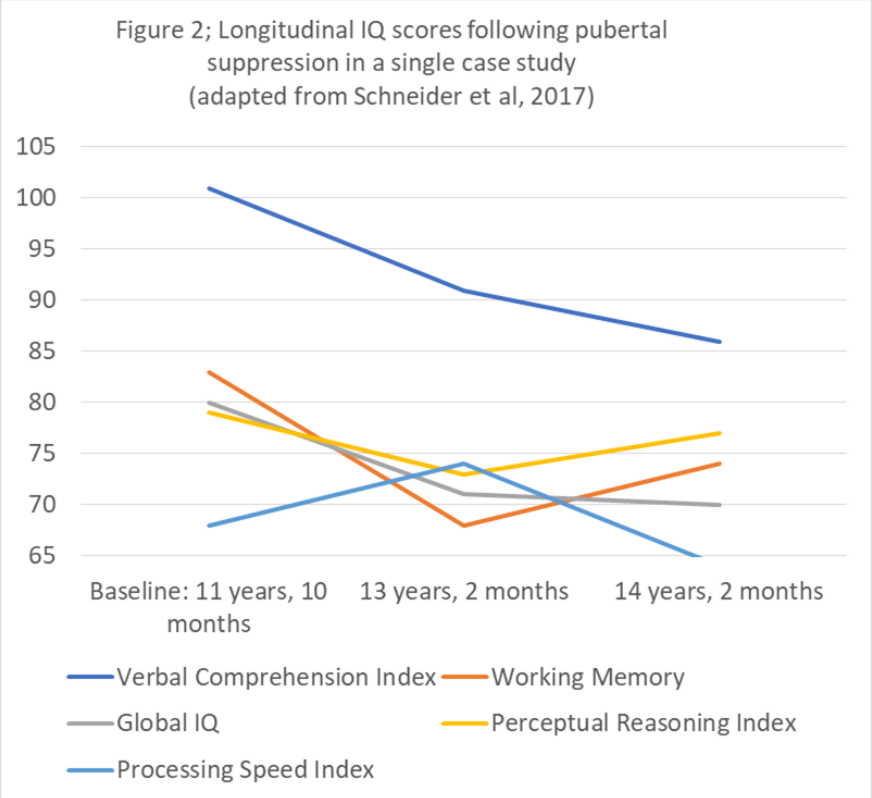
Wojniusz et al, (2016) compared the neuropsychological function of 15 girls with central precocious puberty (CPP) (mean age 10.4 years; range 9.2-11.8) and age matched controls on a very comprehensive battery of neuropsychological tests which yielded 44 scores of function across multiple cognitive domains. All of the girls in the CPP group had been on GnHR analogue treatment for at least 6 months. The authors found no statistically significant differences between the CCP group and controls on any measures with the exception of the Trail Making Number Sequencing Task score. Given that the authors didn't control for multiple comparisons (over 40) and that the groups didn't differ on other tests of processing speed the authors speculate that this finding is "accidental". In their discussion, the authors note that in contrast to previous reports of elevated verbal IQ scores and accelerated school performance in CPP girls [56,57], the IQ in their CCP group was somewhat lower than the controls, although the difference was not statistically significant. It is noteworthy that only 3 of the 12 girls in the Ehrhardt study with idiopathic precocious puberty had been treated with Provera (medroxyprogesterone acetate). Galatzer et al found that the verbal IQ distribution in 52 girls with precocious puberty was two or more times the expected theoretical percentile in the above average area (greater than 110, 56.9% v 25%), and five times more in the very superior area (greater than 130, 10.1% v 2.2%). However the treatment status of the sample is not reported, other than in the final paragraph of the discussion where the authors note that "Another aspect that requires further delineation is the effect of medical treatment of these patients. At present it is common practice to postpone physiologic development with the use of antiandrogen or gonadotrophin-releasing hormone analogues. The impact of these drugs on the intellectual and possibly emotional development of girls with precocious puberty remains to be evaluated". Galatzer et al interpreted their findings as possible evidence of an effect of sex hormones

on brain development, especially on the left hemisphere, during the prepubertal period.

Wojniusz et al state '*both groups (CPP and controls) showed* ***very similar*** (my emphasis) *scores with regard to cognitive performance* '. [58]. This conclusion was questioned by Hayes (2017) who noted that the authors discussion of their findings minimised the substantial difference in IQ scores between the groups (7 points) by overemphasizing the lack of statistical significance in the small sample (p=0.09) and ignoring the clinical difference between someone functioning at the 55thcentile and someone at the 34th centile[59].

GnHR analogues and Transgender and Gender Diverse Young People

Three studies were identified that examined the neuropsychological impact of GnHR treatment in transgender and gender diverse young people. In a single case study, Schneider et al (2017) examined the impact of pubertal suppression on brain white matter and (white matter fractional anisotropy) and cognitive function (Wechsler Intelligence Scale for Children-IV) in an 11-year-old treated for gender dysphoria (male-to-female). On admission, at the age of 11 years and 10 months, the patient was assessed to have a global IQ of 80. Treatment with GnRHa was instigated at age 11 years, 11 months. The patient was reassessed age 13 and 3 months, at which time, a loss of 9 IQ points had occurred, and the IQ had dropped to 71. A loss of 15 points was evident in working memory. At 14 years and 2 months a loss of 10 global IQ points and 9 points in working memory remained apparent. The verbal comprehension index (a measure which depends on the expansion of vocabulary and conceptual thinking in adolescence, for the standardised score to remain stable) deteriorated progressively over the follow up, falling from the initial baseline of 101, to 91 (age 13) and 86 (age 14), a loss of 15 points over 3 years [60]. See Figure 2.



In a cross sectional design, Staphorsius et al., 2015 compared the performance of GnHR treated (8 male-to female; 12 female-to male) and untreated transgender adolescents (10 male-to-female; 10 female-to-male)

on the Tower of London Test (a test of executive function tapping the ability to strategize). No baseline measure of function was taken. The subjects also completed four subscales of the Wechsler Intelligence Scales (arithmetic, vocabulary picture arrangement and block design) and tests of mental rotation and face recognition. Only IQ, and accuracy and timed scores from the Tower of London Test are reported. The groups were not matched for IQ, with control males functioning at a significantly higher level than the suppressed male-to-female group. No results for the tests of mental rotation or face recognition are reported (but are promised in a later publication). Whilst the groups did not differ with respect to reaction time on the Tower of London Test, suppressed male-to-females had significantly lower accuracy scores compared to the control groups. This pattern remained significant after controlling for IQ. Despite this, the reaction-time finding has been subsequently been reported as evidence for no detrimental effects on performance in citations in the subsequent literature [55] and in policy documents [62].

Arnoldussen et al., (2022) reported the results of an assessment of IQ, before the commencement of GnRH analogue treatment in 72 children and examined the relationship between this measure and a highly simplified, dichotomised index of educational progress/achievement ('vocational educated' vs 'higher vocational educated/academic educated'). Prior to treatment, the mean and standard deviation of the IQ score in the group was comparable to the general population (mean =100, standard deviation =15). Forty percent of the eligible subjects declined to participate in the follow-up. No conclusions can be drawn from this study with respect to the impact of puberty suppression on the development of cognitive function.

Discussion

The synthesis of findings from multiple fields of study (neurodevelopment, neuroimaging, neuroendocrinology) indicates an association between GnRH expression and brain function and structure. Despite the broad and multidisciplinary knowledge base which indicates disruption of GnRH expression is likely to have an impact on cognitive function, and explicit calls in the literature for this to be studied that date back three decades [56] there have been no human studies to date that have systematically explored the impact of these treatments on neuropsychological function with an adequate baseline and follow up.

Whilst no means conclusive due to the poor quality of evidence, studies examining the impact of puberty suppression in young people indicate a possible detrimental impact on IQ [59,60,64]. These findings concord with the wider literature on GnRH expression and brain structure and function. Studies in mice, sheep and primates indicate an impact of GnRH suppression on behavioural analogues of cognitive function, effects that are often sex specific. Whilst there is some evidence that indicates pubertal suppression may impact cognitive function, there is no evidence to date to support the oft cited assertion that the effects of puberty blockers are fully reversible [62,65]. Indeed, the only study to date that has addressed this in sheep, suggests that this is not the case [51].

Vague hints from poor quality studies are insufficient to allow people considering these treatments to make an informed decision regarding the possible impact on their neuropsychological function. Critical questions remain unanswered regarding the nature, extent and permanence of any arrested development of cognitive function that may be associated with pharmacological blocking of puberty. If cognitive development 'catches up' following the discontinuation of puberty suppression, how long does this take and is the recovery complete? Several animal studies indicate that some cognitive effects may be sex specific[30,46,54] consistent with imaging studies in adolescents which indicate different trajectories of neurodevelopment in males and females [31] . Natal sex must therefore be a critical variable of interest in future research designs. How does subsequent treatment with cross sex hormones influence neuropsychological development following puberty suppression? Given the very high proportion of patients who proceed to treatment with cross sex hormone following treatment with puberty blockers [66], it is critical that research designs utilise the narrow window before introducing same sex hormone to assess impact. What impact does any delay in cognitive development have on an individual's educational trajectory and subsequent life opportunities given the critical educational window in which these treatments are typically prescribed? Longitudinal studies are urgently needed to study the educational and vocational trajectories of people undergoing these treatments.

The importance of an adequate baseline prior to treatment when assessing the impact of puberty blocking agents on neuropsychological function cannot be overstated given the multiple vulnerabilities associated with gender identity disorder. Many conditions which are likely to compromise cognitive function are overrepresented in this population[67,68]. Neurodiversity is overrepresented in TGD people, who are three to six times more likely to have a diagnosis of autism than their peers [67]. Attention deficit hyperactivity disorder is also overrepresented in this group. In addition to increased representation of neurodiverse conditions, the rates of mental health difficulties in this population are high, with adolescents seeking gender affirming treatments presenting with psychiatric symptoms and disorders comparable to those seen among adolescent psychiatric patients [68]. All of these conditions are known to compromise neuropsychological function and future study designs must take this into consideration. Even without a psychiatric comorbidity, the psychosocial stresses associated with living with gender dysphoria as a young person can be very significant and would be expected to have a substantial impact on cognitive reserve. This would be consistent with the findings of Haraldsen [69] who in a conference presentation, reported highly significant differences between gender identity disorder patients and controls on measures of verbal and executive function with significantly atrophic hippocampal and cerebellum tissue *prior* to any treatment with puberty blocking agents. A recent study from Turkey reported significantly worse performance on tests of response inhibition and verbal fluency in 22 adolescents with gender dysphoria compared to controls, with no group differences in set shifting. None of the patients in the gender dysphoria group had taken gender affirming treatment at the time of the assessment, but levels of comorbid psychiatric disturbance were high with 72.7% having at least one psychiatric diagnosis[70]. This is consistent with earlier findings from the same group indicating more disturbed behaviour related to executive function and social impairment in children with gender dysphoria compared to controls [71]. The impact of blocking puberty in a brain that may already be developing in an atypical trajectory is unknown.

Subsequent follow-up should monitor development not just during and at the end of treatment, but to at least age 25, when neurodevelopment begins to complete [72]. Scores from single tests, in single domains tell us very little when they are presented and examined in isolation from the wider neuropsychological profile of the patient. Given that the impact of pubertal suppression on cognitive function is very likely to be governed to some extent by the pubertal stage at which it is commenced, broader indices of abnormality across a profile may be more illuminating than multiple individual comparisons between tests in specific cognitive domains. This will require administering a comprehensive test battery and indices such as the number of test scores outside the expected range, and indices of consistency across domains and other patterns indicative of wider abnormalities may be illuminating. As recommended by Ludvigsson et al, (2023), analyses which include measures of intra individual change may be more useful than group level analyses, particularly given the selection bias and high dropout rates of participants in these studies. Whilst randomised control trials may be difficult to conduct, controls should nevertheless be an integral part of a research protocol, with some thought given to the significant mental health comorbidities often reported by patients seeking these treatments and the independent impacts these exert on cognitive function (see above).

Despite the evidence base that indicates cognition is an important area to consider in the study of outcomes following pubertal suppression, it is an area that clinical neuropsychologists have largely neglected to date. The reasons for this are likely to be multifactorial and reflect to some degree the historical factors related to the introduction of this 'off label' treatment for TDG adolescents. The current, highly polarised socio-political atmosphere that surrounds much of the research published in this area may also make some academics wary about conducting and publishing research in this field [73,74]Whatever the reasons, the evidence base has not kept pace with the growth of the treatment [3] and TGD people have been poorly served by the absence of research in this area, which is urgently needed given the increasing numbers of young people seeking these treatments.

From a clinical perspective, a multidisciplinary approach is recognised as the gold standard in the assessment and monitoring pharmacological treatments for TGD young people [75–77]. The results from this scoping review indicate that clinical neuropsychologists should be an integral members of this clinical team, providing a comprehensive neuropsychological baseline against which change can be measured in the future, monitoring change over time and providing clinical input to address any neuropsychological concerns, if and when they

arise.

Declarations

Competing interest : A summary of this review was presented by the author at the Society for Evidence Based Gender Medicine Meeting in New York in October 2023. No funding has been received for the preparation of this manuscript.

		Animal Model	Study Design
1	Wojnius et al., 2011	Male & female sheep	N=48 same sex twin pairs GnRHa treated group (twin 1) vs untr
2	Evans et al., 2012	Male & female sheep	N=46 same sex twin pairs GnRHa treated group (twin 1) vs untr
3	Nuruddin et al,. 2013	Male & female sheep	N=30 same sex twin pairs (14 female/16 male) GnRHa treated gr
4	Nuruddin et al, 2013	Male and female sheep	41 brains of sheep from the experiment described above 17 treate
5	Wojniusz et al, 2013	Male and female Sheep	N=46 twin pairs GnRHa treated group (twin 1) vs untreated con
6	Hough et al, 2017a	Male Sheep	Group 1. GnRH and testosterone blocked n= 49 Group 2. GnRH
7	Hough et al, 2017b	Male Sheep (as above)	Group 1. GnRHa treated until 44 weeks of age n=25 (Twin 1) Gr
8	Hough et al, 2019	Male Sheep	Group 1. GnRH and testosterone blocked (n=55) Group 2. GnRI
9	Anacker et al, 2021	Male and female mice	Control vs GnRA injected mice
10	Pincus et al, 2021	Female Macaque Monkeys	GnRHa treated n=34 Controls n=36
11	Godfrey 2023 et al	Rhesus macque monkeys	GnRHa treated N=23 Controls n=22

References

1. Lee JY, Rosenthal SM. Gender-Affirming Care of Transgender and Gender-Diverse Youth: Current Concepts. *Annu Rev Med* . 2023;74:107-116. doi:10.1146/ANNUREV-MED-043021-032007

2. de Graaf NM, Giovanardi G, Zitz C, Carmichael P. Sex Ratio in Children and Adolescents Referred to the Gender Identity Development Service in the UK (2009–2016). *Arch Sex Behav* . 2018;47(5):1301-1304. doi:10.1007/S10508-018-1204-9/METRICS

3. Ludvigsson JF, Adolfsson J, Höistad M, Rydelius P-A, Kriström B, Landén M. A systematic review of hormone treatment for children with gender dysphoria and recommendations for research. *Acta Paediatr* . April 2023. doi:10.1111/APA.16791

4. Blakemore S-J, Choudhury S. Development of the adolescent brain: implications for executive function and social cognition. *J Child Psychol Psychiatry Allied Discip* . 2006;47(3):296-312. doi:10.1111/j.1469-7610.2006.01611.x

5. Meethal SV. The role of hypothalamic-pituitary-gonadal hormones in the normal structure and functioning of the brain. *Cell Mol Life Sci* . 2005;62(3):257-270. doi:https://dx.doi.org/10.1007/s00018-004-4381-3 PT - Review

6. Yang D, Zhang W, Zhu Y, et al. Initiation of the hypothalamic-pituitary-gonadal axis in young girls undergoing central precocious puberty exerts remodeling effects on the prefrontal cortex. Abreu Kaiser, UB, Achenbach, TM, Ruffle, TM, Araki, R, Ago, Y, Hasebe, S, Nishiyama, S, Tanaka, T, Oka, S, et al., Argyropoulou, MI, Kiortsis, DN, Bajaj, S, Raikes, A, Smith, R, Dailey, NS, Alkozei, A, Vanuk, JR, et al., Brouwer, RM, Koenis, MM, Schnack, AP, ed. *Front Psychiatry* . 2019;10. doi:https://dx.doi.org/10.3389/fpsyt.2019.00332

7. Chen T, Lu Y, Wang Y, et al. Altered Brain Structure and Functional Connectivity Associated with Pubertal Hormones in Girls with Precocious Puberty. Oldehinkel Verhulst, F. C., Ormel, J., Goddings, A. L., Burnett Heyes, S., Bird, G., Viner, R. M., Blakemore, S. J., Puga-Olguin, A., Rodriguez-Landa, J. F., Rovirosa-Hernandez, M. J., et al., Aron, A. R., Monsell, S., Sahakian, B. J., Robbins, T. W., Be AJ, ed. *Neural Plast* . 2019;2019:1465632. doi:https://dx.doi.org/10.1155/2019/1465632

8. Zhou L, Chen T, Wang Y, et al. Influence of the hypothalamus-pituitary-gonadal axis reactivation and pubertal hormones on gray matter volume in early pubertal girls. *Int J Neurosci* . 2020;131(10):946-952. doi:https://dx.doi.org/10.1080/00207454.2020.1763342 PT - Article

9. Chen D, Strang JF, Kolbuck VD, et al. Consensus Parameter: Research Methodologies to Evaluate Neurodevelopmental Effects of Pubertal Suppression in Transgender Youth. *Transgender Heal* . 2020;5(4):246-257. doi:10.1089/TRGH.2020.0006

10. Hough D, Robinson JE, Bellingham M, et al. Peripubertal GnRH and testosterone co-treatment leads to increased familiarity preferences in male sheep. Armstrong Caunt, C.J., Finch, A.R., McArdle, C.A., Berenbaum, S.A., Beltz, A.M., Bhasin, S., Yuan, Q.X., Steiner, B.S., Swerdloff, R.S., Blair, J.A., McGee, H., Bhatta, S., Palm, R., Casadesus, G., Carel, J.C., Eugster, E.A., Rogol, A., Ghizzoni, L., Pal SP, ed. *Psychoneuroendocrinology* . 2019;108:70-77. doi:https://dx.doi.org/10.1016/j.psyneuen.2019.06.008

11. Nuruddin S, Krogenaes A, Brynildsrud OB, et al. Peri-pubertal gonadotropin-releasing hormone agonist treatment affects sex biased gene expression of amygdala in sheep. Albertson Navratil, A., Mignot, M., Dufourny, L., Cherrington, B., Skinner, D.C., Anagnostou, E., Taylor, M., Bao, A.M., Swaab, D.F., Benjamini, Y., Hochberg, Y., Beyenburg, S., Watzka, M., Clusmann, H., Blumcke, I., Bidlingmaier, F., Elger, C.E., Stoffe AJ, ed. *Psychoneuroendocrinology* . 2013;38(12):3115-3127. doi:https://dx.doi.org/10.1016/j.psyneuen.2013.09.011 PT - Article

12. Skinner DC, Albertson AJ, Navratil A, et al. Effects of Gonadotrophin-Releasing Hormone Outside the Hypothalamic-Pituitary-Reproductive Axis. *J Neuroendocrinol* . 2009;21(4):282-292. doi:10.1111/J.1365-2826.2009.01842.X

13. Hensch TK, Bilimoria PM. Re-opening Windows: Manipulating Critical Periods for Brain Development. *Cerebrum Dana Forum Brain Sci* . 2012;2012:11. /pmc/articles/PMC3574806/. Accessed April 17, 2023.

14. Ismail FY, Fatemi A, Johnston M V. Cerebral plasticity: Windows of opportunity in the developing brain. *Eur J Paediatr Neurol* . 2017;21(1):23-48. doi:10.1016/j.ejpn.2016.07.007

15. Wiesel TN. Postnatal development of the visual cortex and the influence of environment. *Nature* . 1982;299(5884):583-591. doi:10.1038/299583A0

16. Soliman A, De Sanctis V, Elalaily R. Nutrition and pubertal development. *Indian J Endocrinol Metab* . 2014;18:S39-S47. doi:10.4103/2230-8210.145073

17. Hartshorne JK, Tenenbaum JB, Pinker S. A critical period for second language acquisition: Evidence from 2/3 million English speakers. *Cognition* . 2018;177:263. doi:10.1016/J.COGNITION.2018.04.007

18. Hensch TK. Critical period plasticity in local cortical circuits. *Nat Rev Neurosci* . 2005;6(11):877-888. doi:10.1038/NRN1787

19. Shonkoff J., Phillips DA. From Neurons to Neighborhoods: The Science of Early Childhood Development. *From Neurons to Neighborhoods* . November 2000. doi:10.17226/9824

20. Hensch TK. Critical period regulation. *Annu Rev Neurosci* . 2004;27:549-579. doi:10.1146/ANNUREV.NEURO.27.070203.144327

21. Kilford EJ, Garrett E, Blakemore SJ. The development of social cognition in adolescence: An integrated perspective. *Neurosci Biobehav Rev* . 2016;70:106-120. doi:10.1016/J.NEUBIOREV.2016.08.016

22. Eroglu C, Barres BA. Regulation of synaptic connectivity by glia. *Nature* . 2010;468(7321):223-231. doi:10.1038/NATURE09612

23. Vanderhaeghen P, Cheng HJ. Guidance Molecules in Axon Pruning and Cell Death. *Cold Spring Harb Perspect Biol* . 2010;2(6). doi:10.1101/CSHPERSPECT.A001859

24. de Graaf-Peters VB, Hadders-Algra M. Ontogeny of the human central nervous system: What is happening when? *Early Hum Dev* . 2006;82(4):257-266. doi:10.1016/J.EARLHUMDEV.2005.10.013

25. Maxwell Cowan W, Fawcett JW, O'Leary DDM, Stanfield BB. Regressive events in neurogenesis. *Science* . 1984;225(4668):1258-1265. doi:10.1126/SCIENCE.6474175

26. Yuan J, Lipinski M, Degterev A. Diversity in the mechanisms of neuronal cell death. *Neuron* . 2003;40(2):401-413. doi:10.1016/S0896-6273(03)00601-9

27. Changeux JP, Danchin A. Selective stabilisation of developing synapses as a mechanism for the specification of neuronal networks.*Nat 1976 2645588* . 1976;264(5588):705-712. doi:10.1038/264705a0

28. Petanjek Z, Judaš M, Šimić G, et al. Extraordinary neoteny of synaptic spines in the human prefrontal cortex. *Proc Natl Acad Sci U S A* . 2011;108(32):13281-13286. doi:10.1073/PNAS.1105108108/-/DCSUPPLEMENTAL/PNAS.201105108SI.PDF

29. Huttenlocher P. Synaptic density in human frontal cortex - developmental changes and effects of aging. *Brain Res* . 1979;163(2):195-205. doi:10.1016/0006-8993(79)90349-4

30. Benes FM, Turtle M, Khan Y, Farol P. Myelination of a Key Relay Zone in the Hippocampal Formation Occurs in the Human Brain During Childhood, Adolescence, and Adulthood. *Arch Gen Psychiatry* . 1994;51(6):477-484. doi:10.1001/ARCHPSYC.1994.03950060041004

31. Giedd JN, Raznahan A, Mills KL, Lenroot RK. Review: magnetic resonance imaging of male/female differences in human adolescent brain anatomy. *Biol Sex Differ* . 2012;3(1):19. doi:10.1186/2042-6410-3-19

32. Ojha A, Parr AC, Foran W, Calabro FJ, Luna B. Puberty contributes to adolescent development of fronto-striatal functional connectivity supporting inhibitory control. *Dev Cogn Neurosci* . 2022;58:101183. doi:10.1016/J.DCN.2022.101183

33. Ravindranath O, Calabro FJ, Foran W, Luna B. Pubertal development underlies optimization of inhibitory control through specialization of ventrolateral prefrontal cortex. *Dev Cogn Neurosci* . 2022;58. doi:10.1016/J.DCN.2022.101162

34. Delevich K, Klinger M, Okada NJ, Wilbrecht L. Coming of age in the frontal cortex: The role of puberty in cortical maturation. *Semin Cell Dev Biol* . 2021;118:64-72. doi:10.1016/J.SEMCDB.2021.04.021

35. Goddings AL, Beltz A, Peper JS, Crone EA, Braams BR. Understanding the Role of Puberty in Structural and Functional Development of the Adolescent Brain. *J Res Adolesc* . 2019;29(1):32-53. doi:10.1111/JORA.12408

36. Afroz S, Parato J, Shen H, Smith SS. Synaptic pruning in the female hippocampus is triggered at puberty by extrasynaptic GABAA receptors on dendritic spines. *Elife* . 2016;5(MAY2016). doi:10.7554/ELIFE.15106

37. Yang D, Zhang W, Zhu Y, et al. Initiation of the hypothalamic-pituitary-gonadal axis in young girls undergoing central precocious puberty exerts remodeling effects on the prefrontal cortex.*Front Psychiatry* . 2019;10(MAY):332. doi:https://dx.doi.org/10.3389/fpsyt.2019.00332 PT - Article

38. Shirazi TN, Self H, Cantor J, et al. Timing of peripubertal steroid exposure predicts visuospatial cognition in men: Evidence from three samples. Adkins-Regan Altemus, M., Sarvalya, N., Epperson, C.N., Angold, A., Costello, E.J., Worthman, C.M., Apter, D., Bakker, J., Honda, S., Harada, N., Balthazart, J., Barona, A., Reynolds, C.R., Chastain, R., Becker, J.B., Hu, M., Beltz, A.M., Berenbaum, S.A. E, ed. *Horm Behav* . 2020;121. doi:https://dx.doi.org/10.1016/j.yhbeh.2020.104712

39. Yu W, Chen T, Xia Y, et al. Frequency-dependent alterations in regional homogeneity associated with puberty hormones in girls with central precocious puberty: A resting-state fMRI study. *J Affect Disord* . 2023. doi:https://dx.doi.org/10.1016/j.jad.2023.03.051 PT - Article

40. Spear LP. Adolescent Neurodevelopment. *J Adolesc Heal* . 2013;52(2):S7-S13. doi:10.1016/J.JADOHEALTH.2012.05.006

41. Duijvenvoorde ACK van, Huizenga HM, Somerville LH, et al. Neural Correlates of Expected Risks and Returns in Risky Choice across Development. *J Neurosci* . 2015;35(4):1549-1560. doi:10.1523/JNEUROSCI.1924-14.2015

42. Casey BJ, Getz S, Galvan A. The adolescent brain. *Dev Rev* . 2008;28(1):62. doi:10.1016/J.DR.2007.08.003

43. Knoll LJ, Magis-Weinberg L, Speekenbrink M, Blakemore S-JJ. Social Influence on Risk Perception During Adolescence: *Psychol Sci* . 2015;26(5):583-592. doi:10.1177/0956797615569578

44. Somerville LH. The Teenage Brain: Sensitivity to Social Evaluation. *Curr Dir Psychol Sci* . 2013;22(2):121-127. doi:10.1177/0963721413476512

45. Hartley CA, Somerville LH. The neuroscience of adolescent decision-making. *Curr Opin Behav Sci* . 2015;5:108. doi:10.1016/J.COBEHA.2015.09.004

46. Wojniusz S, Vögele C, Ropstad E, et al. Prepubertal gonadotropin-releasing hormone analog leads to exaggerated behavioral and emotional sex differences in sheep. Andreano Cahill, L., Appelhans, B.M., Luecken, L.J., Baum, M.J., Berntson, G.G., Quigley, K.S., Jang, J.F., Boysen, S.T., Boissy, A., Bouix, J., Orgeur, P., Poindron, P., Bibe, B., Le Neindre, P., Bryan, K.J., Mudd, J.C., Richardson, S.L., Chang, J., Lee JM, ed. *Horm Behav* . 2011;59(1):22-27. doi:https://dx.doi.org/10.1016/j.yhbeh.2010.09.010

47. Evans NP, Robinson JE, Erhard HW, Ropstad E, Fleming LM, Haraldsen IRH. Development of psychophysiological motoric reactivity is influenced by peripubertal pharmacological inhibition of gonadotropin releasing hormone action - Results of an ovine model. Albertson Navratil, A., Mignot, M., Dufourny, L., Cherrington, B., Skinner, D.C., Andreano, J.M., Waisman, J., Donley, L., Cahill, L., Archer, J., Arnold, S., Hubler, M., Reichler, I., Boissy, A., Boissy, A., Arnould, C., Chaillou, E., Desire, L., Duvaux AJ, ed. *Psychoneuroendocrinology* . 2012;37(11):1876-1884. doi:https://dx.doi.org/10.1016/j.psyneuen.2012.03.020

48. Nuruddin S, Bruchhage M, Ropstad E, et al. Effects of peripubertal gonadotropin-releasing hormone agonist on brain development in sheep- A magnetic resonance imaging study. *Psychoneuroendocrinology* . 2013;38(10):1994-2002. doi:10.1016/j.psyneuen.2013.03.009

49. Wojniusz S, Ropstad E, Evans N, et al. Sex-specific development of spatial orientation is independent of peripubertal gonadal steroids. *Psychoneuroendocrinology* . 2013;38(9):1709-1716. doi:10.1016/j.psyneuen.2013.02.005

50. Hough D, Bellingham M, Haraldsen IRHH, et al. Spatial memory is impaired by peripubertal GnRH agonist treatment and testosterone replacement in sheep. Aikey Nyby, J.G., Anmuth, D.M., James, P.J., Albertson, A.J., Navratil, A., Mignot, M., Dufourny, L., Cherrington, B., Skinner, D.C., Armstrong, S.P., Caunt, C.J., Finch, A.R., McArdle, C.A., Benke, T.A., Luthi, A., Isaac, J.T.R., Collingridge, G.L., Ber JL, ed. *Psychoneuroendocrinology* . 2017;75:173-182. doi:https://dx.doi.org/10.1016/j.psyneuen.2016.10.016

51. Hough D, Bellingham M, Haraldsen IR, et al. A reduction in long-term spatial memory persists after discontinuation of peripubertal GnRH agonist treatment in sheep. Albertson Navratil, A., Mignot, M., Dufourny, L., Cherrington, B., Skinner, D.C., Beer, T.M., Bland, L.B., Bussiere, J.R., Neiss, M.B., Wersinger, E.M., Garzotto, M., Ryan, C.W., Janowsky, J.S., Caraty, A., Skinner, D.C., Carel, J.C., Eugster, E.A., Rogo AJ, ed. *Psychoneuroendocrinology* . 2017;77:1-8. doi:https://dx.doi.org/10.1016/j.psyneuen.2016.11.029

52. Pincus M, Godfrey JR, Feczko E, et al. Chronic psychosocial stress and experimental pubertal delay affect socioemotional behavior and amygdala functional connectivity in adolescent female rhesus macaques. Bickart Hollenbeck, M.C., Barrett, L.F., Dickerson, B.C., Bourke, C.H., Neigh, G.N., Breach, M.R., Moench, K.M., Wellman, C.L., Cohodes, E.M., Kitt, E.R., Baskin-Sommers, A., Gee, D.G., Coleman, K., Robertson, N.D., Bethea, C.L., Copeland, W.E., Worthman KC, ed. *Psychoneuroendocrinology* . 2021;127:105154.

doi:https://dx.doi.org/10.1016/j.psyneuen.2021.105154

53. Godfrey JRJ, Howell BR, Mummert A, et al. Effects of social rank and pubertal delay on brain structure in female rhesus macaques. Albert Newhouse, P.A., Amaral, D.G., Bassett, J.L., Andersen, S.L., Andersen, S.L., Tomada, A., Vincow, E.S., Valente, E., Polcari, A., Teicher, M.H., Anderson, S.A., Classey, J.D., Conde, F., Lund, J.S., Lewis, D.A., Angold, A., Costello, E.J., Erkanli, KM, ed.*Psychoneuroendocrinology* . 2023;149:105987. doi:https://dx.doi.org/10.1016/j.psyneuen.2022.105987 PT - Article

54. Anacker C, Sydnor E, Chen BK, et al. Behavioral and neurobiological effects of GnRH agonist treatment in mice-Potential implications for puberty suppression in transgender individuals. Abramowitz Anacker, C., Hen, R., Anacker, C., Luna, V.M., Stevens, G.S., Millette, A., Shores, R., Jimenez, J.C., et al., Anacker, C., Scholz, J., O'Donnell, K.J., Allemang-Grand, R., Diorio, J., Bagot, R.C., et al., Blasco-Serra, A., Gonzalez-Soler, E.M J, ed. *Neuropsychopharmacology* . 2021;46(5):882-890. doi:https://dx.doi.org/10.1038/s41386-020-00826-1

55. Brik T, Vrouenraets LJ., de Vries MC, Hannema SE. Trajectories of Adolescents Treated with Gonadotropin-Releasing Hormone Analogues for Gender Dysphoria. *Arch Sex Behav* . 2020;49(7):2611-2618. doi:10.1007/S10508-020-01660-8/FIGURES/1

56. Galatzer A, Beth-Halachmi N, Kauli R, Laron Z. Intellectual function of girls with precocious puberty. *Pediatrics* . 1984;74(2):246-249. doi:10.1542/peds.74.2.246

57. Ehrhardt AA, Meyer-Bahlburg HFL. Idiopathic precocious puberty in girls: long-term effects on adolescent behavior. *Acta Endocrinol Suppl (Copenh)* . 1986;279(279):247-253. doi:10.1530/ACTA.0.112S247

58. Wojniusz S, Callens N, Sütterlin S, et al. Cognitive, Emotional, and Psychosocial Functioning of Girls Treated with Pharmacological Puberty Blockage for Idiopathic Central Precocious Puberty. Appelhans Luecken, L. J., Atkinson, L., Yoshida, G., Biro, F. M., Greenspan, L. C., Galvez, M. P., Pinney, S. M., Teitelbaum, S., Windham, G. C., et al., Bishop, S., Duncan, J., Brett, M., Lawrence, A. D., Carel, J. C., Eugster, E. A., Rogol, A., Ghizzon BM, ed. *Front Psychol* . 2016;7(JUL):1053. doi:https://dx.doi.org/10.3389/fpsyg.2016.01053

59. Hayes P. Commentary: Cognitive, Emotional, and Psychosocial Functioning of Girls Treated with Pharmacological Puberty Blockage for Idiopathic Central Precocious Puberty. Bouvattier Coste, J., Rodrigue, D., Teinturier, C., Carel, J. C., Chaussain, J. L., et al., Cassio, A., Cacciari, E., Balsamo, A., Bal, M., Tassinari, D., Hayes, P., Hough, D., Bellingham, M., Haraldsen, I. R., McLaughlin, M., Robinson, J. E., Solbakk, A C, ed. *Front Psychol* . 2017;8. doi:10.3389/fpsyg.2017.00044

60. Schneider M. A, Spritzer P. M, Soll BM. MB, et al. Brain maturation, cognition and voice pattern in a gender dysphoria case under pubertal suppression. *Front Hum Neurosci* . 2017;11:528. doi:10.3389/fnhum.2017.00528

61. Staphorsius AS, Kreukels BPC, Cohen-Kettenis PT, et al. Puberty suppression and executive functioning: An fMRI-study in adolescents with gender dysphoria. Achenbach Edelbrock, C.S., Albert, D., Steinberg, L., American Psychiatric Association, American Psychiatric Association, Asato, M.R., Sweeney, J.A., Luna, B., Ashburner, J., Baker, S.C., Rogers, R.D., Owen, A.M., Frith, C.D., Dolan, R.J., Frackowiak, R. TM, ed. *Psychoneuroendocrinology* . 2015;56:190-199. doi:https://dx.doi.org/10.1016/j.psyneuen.2015.03.007

62. NHS England. Journal of Child Psychology and Psychiatry and Allied Disciplines.Clinical Commissioning Policy: Prescribing of Cross-Sex Hormones as part of the Gender Identity Development Service for Children and Adolescents. *Clin Comm Policy 16046/P* . 2016. https://www.england.nhs.uk/wp-content/uploads/2018/07/Prescribing-of-cross-sex-hormones-as-part-of-the-gender-identity-development-service-for-children-and-adolesce.pdf. Accessed April 21, 2023.

63. Arnoldussen M, Hooijman EC, Kreukels BP, Lc De Vries A. Association between pre-treatment IQ and educational achievement after gender-affirming treatment including puberty suppression in transgender adolescents. *Clin Child Psychol Psychiatry* . 2022;27(4):1069-1076. doi:10.1177/13591045221091652

64. Mul D, Versluis-den Bieman HJM, Slijper FM. E, Oostdijk W, Waelkens, J., Drop S. Psychological assessments before and after treatment of early puberty in adopted children. *ACTA Paediatr* . 2001;90(9):965-971. doi:https://dx.doi.org/10.1080/080352501316978011 PT - Article

65. Panagiotakopoulos L. Transgender medicine - puberty suppression.*Rev Endocr Metab Disord* . 2018;19(3):221-225. doi:https://dx.doi.org/10.1007/s11154-018-9457-0 PT - Review

66. de Vries ALCC, Steensma TD, Doreleijers TAHH, Cohen-Kettenis Thomas D.; ORCID: https://orcid.org/0000-0003-1330-3644 PTAI-S, Cohen-Kettenis PT. Puberty suppression in adolescents with gender identity disorder: A prospective follow-up study. American Psychiatric Association P. T., Delemarre-van de Waal, H. A., Gooren, L. J., Cohen-Kettenis, P. T., Owen, A., Kaijser, V. G., Bradley, S. J., Zucker, K. J., Cohen-Kettenis, P. T., Goozen, van, S. H., Cohen-Kettenis, P. T., Goozen, van, S. H., Coh C-K, ed. *J Sex Med* . 2011;8(8):2276-2283. doi:https://dx.doi.org/10.1111/j.1743-6109.2010.01943.x

67. Warrier V, Greenberg DM, Weir E, et al. Elevated rates of autism, other neurodevelopmental and psychiatric diagnoses, and autistic traits in transgender and gender-diverse individuals. *Nat Commun* . 2020;11(1). doi:10.1038/S41467-020-17794-1

68. Karvonen M, Karukivi M, Kronström K, Kaltiala R. The nature of co-morbid psychopathology in adolescents with gender dysphoria.*Psychiatry Res* . 2022;317:114896. doi:10.1016/J.PSYCHRES.2022.114896

69. Haraldsen I. Early onset gid and its effects on hippocampus measured by neuropsychological tests and MRI. *J Sex Med* . 2011;8(SUPPL. 3):106. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=70578674.

70. Gözde Yazkan Akgül Burcu Yıldırım Budak NPF, Yıldırım ABE. Executive functions in adolescents with gender dysphoria. *Appl Neuropsychol Child* . 2023;0(0):1-6. doi:10.1080/21622965.2023.2270096

71. Akgül GY, Ayaz AB, Yildirim B, Fis NP. Autistic Traits and Executive Functions in Children and Adolescents With Gender Dysphoria. *J Sex Marital Ther* . 2018;44(7). doi:10.1080/0092623X.2018.1437489

72. Arain M, Haque M, Johal L, et al. Maturation of the adolescent brain. *Neuropsychiatr Dis Treat* . 2013. doi:10.2147/NDT.S39776

73. Bailey JM. How to Ruin Sex Research. *Arch Sex Behav* . 2019;48(4):1007-1011. doi:10.1007/S10508-019-1420-Y/METRICS

74. Singal J. The media is spreading bad trans science - UnHerd. *Unherd* . https://unherd.com/2023/04/the-media-is-spreading-bad-trans-science/. Published 2023. Accessed April 22, 2023.

75. Fisher A., G. S, C. C. Gender Dysphoria: Management in the Transition age. *Trends Androl Sex Med* . 2021:255-264. doi:https://dx.doi.org/10.1007/978-3-030-80015-4_14 PT - Chapter

76. Kyriakou A, Nicolaides NC, Skordis N. Current approach to the clinical care of adolescents with gender dysphoria. *Acta Biomed* . 2020;91(1):165-175. doi:10.23750/abm.v91i1.9244

77. Cass H. Cass Review – Independent Review of Gender Identity Services for Children and Young People. 2021. https://cass.independent-review.uk/. Accessed April 22, 2023.

PRISMA flow diagram for systematic reviews which included searches of databases, registers and other sources: Search terms: GnRH*' or 'Lupron' AND 'Pubert*' and any of the following Neuropsychological Terms: Cogniti*, OR Neuropsychol*, OR 'Executive', OR 'Language', OR 'Memory', OR 'Learning', OR 'Spatial', OR 'Intelligence', OR 'IQ', OR 'Processing', OR 'Attention', OR 'Social'.