

The Impact of Suppressing Puberty on Neuropsychological Function

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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 pubertal 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 function 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 care¹. 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 puberty⁴⁻⁸ concerns have been raised regarding the impact of medications that interrupt and interfere with this process during this important period of neurodevelopment⁹. In a statement of expert consensus from 24 international specialists 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 memory⁹.

Unsurprisingly, given the critical role of puberty in the development of the brain's anterior regions including the prefrontal cortex⁴, 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 patients¹⁰⁻¹².

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 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 review³, 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 compromised¹⁵. Essential inputs may be internal, for example hormonal or nutritional state¹⁶ and external, for example presence/absence of environmental stimuli¹⁷. 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 cognition²¹.

Adolescence: A Critical Period for Synaptic Pruning & Myelination

The approximate 100 trillion synaptic connections²² 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 synapses²⁷, 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 puberty²⁸. Whilst it was initially thought that synaptic pruning in the cerebral cortex was completed by age 16²⁹ it is now recognised that substantial pruning continues well beyond adolescence and into the third decade of life before stabilizing at the adult level²⁸. 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 females³⁰, 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 responses³³.

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 GnRH 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 study⁵⁴ 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 treatment⁵¹. Significant effects of treatment were also evident on measures of brain structure including overall volume⁵³, functional connectivity⁵² and neuronal density⁵⁴.

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 adolescence³¹. 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 GnRH 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 study⁵⁵. 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.

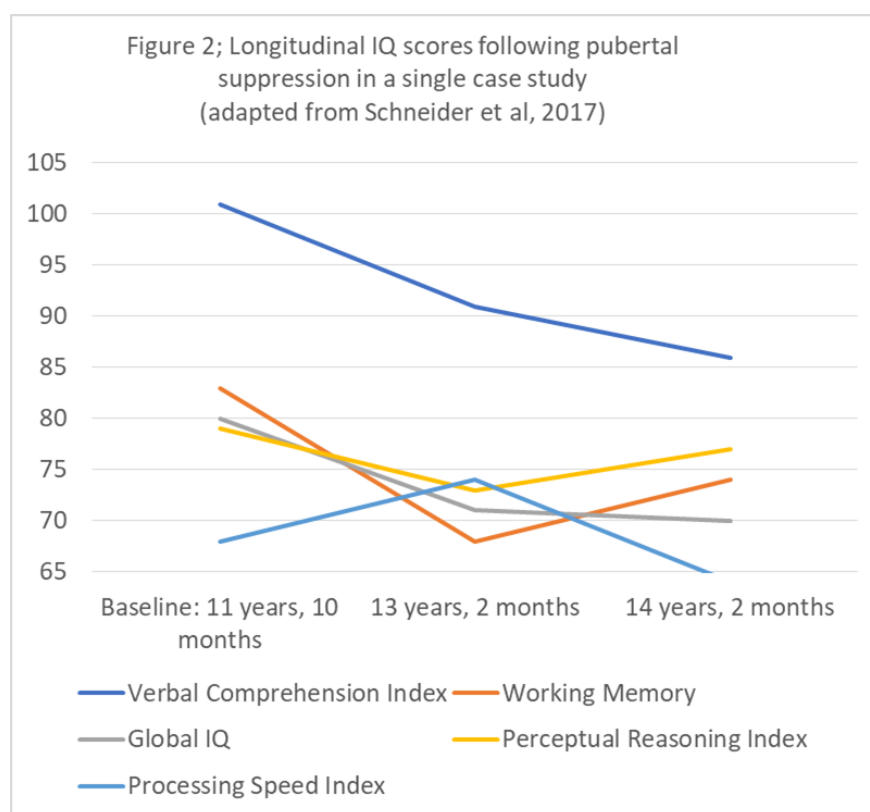
Wojniusz et al, (2016) compared the neuropsychological function of 15 girls with central precocious puberty (CPP) (mean age 10.4 years; range 9.2–11.8) and age matched controls on a very comprehensive battery of neuropsychological tests which yielded 44 scores of function across multiple cognitive domains. All of the girls in the CPP group had been on GnRH 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. In the previous studies that the reference, 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 55th centile and someone at the 34th centile⁵⁹.

GnRH analogues and Transgender and Gender Diverse Young People

Three studies were identified that examined the neuropsychological impact of GnRH 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 years⁶⁰. See Figure 2.



In a cross sectional design, Staphorsius et al., 2015 compared the performance of GnRH 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 peers⁶⁷. 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 patients⁶⁸. 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 Haraldsen⁶⁹ 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 diagnosis⁷⁰. 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 controls⁷¹. 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 complete⁷². 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 treatment³ 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 treat
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) Gn
8	Hough et al, 2019	Male Sheep	Group 1. GnRH and testosterone blocked (n=55) Group 2. GnRH
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

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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'.

