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REVIEW ARTICLE

The impact of suppressing puberty on neuropsychological function: A review

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Abstract

Aim: Concerns have been raised regarding the 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.

Methods: All studies reporting cognitive impacts of treatment with GnRH agonists/antagonists for pubertal suppression in animals or humans were sought via a systematic search strategy across the PubMed, Embase, Web of Science and PsycINFO databases.

Results: Sixteen studies were identified. In mammals, the neuropsychological impacts of puberty blockers are complex and often sex specific ($n = 11$ studies). 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. There is some evidence of a detrimental impact of pubertal suppression on IQ in children.

Conclusion: Critical questions remain unanswered regarding the nature, extent and permanence of any arrested development of cognitive function associated with puberty blockers. The impact of puberal suppression on measures of neuropsychological function is an urgent research priority.

KEYWORDS
gonadotropin-releasing hormone (GnRH), intelligence, memory, puberty, cognition, neurodevelopment, review

1 | 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) agonists or antagonists. 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

Abbreviations: GnRH, Gonadotropin hormone-releasing hormone; GnRHa, GNRH agonists/antagonists; IQ, Intelligence Quotient; TGD, Transgender and Gender Diverse; GIDS, Gender Identity Development Service; MRI, Magnetic Resonance Imaging; fMRI, Functional Magnetic Resonance Imaging; CPP, Central Precocious Puberty.

(GIDS) in the United Kingdom indicate an over 3000% 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 7000% over the 7-year period.

Given the magnitude and complexity of changes that occur in brain function and structure during puberty,[4,5] concerns have been raised regarding the impact of medications that interrupt and interfere with this process during this important period of neurodevelopment.[6] 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 nine 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.[6]

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 highlights learning, memory and emotional processing as relevant areas of neuropsychological interest in outcome studies in these patients.[7–9]

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 and consistency, in this review, trans women/girls are referred to as male-to-female and trans men/boys as female-to-male.

1.1 | 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.[10] 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 (e.g. 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.[11] Essential inputs may be internal, for example, hormonal or nutritional state,[12] and external, for example, the presence/absence of environmental stimuli.[13] 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.[13,14] 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. Adolescence is a critical window of development for executive functions (behavioural and cognitive) and social cognition.[15]

Key notes

- Adolescence is a critical window of neurodevelopment and puberty plays a critical role in these neurodevelopmental processes.
- 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.
- No human studies have systematically explored the neuropsychological impact of pubertal suppression in transgender adolescents with an adequate baseline and follow-up, this is an urgent research priority.

1.2 | Adolescence: A critical period for synaptic pruning & myelination

The approximate 100 trillion synaptic connections 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).[16] 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. 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,[17] 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.[18] It is now recognised that substantial pruning continues well beyond adolescence and into the third decade of life before stabilising at the adult level.[18] 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,[19] 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.[20] 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 grey matter volumes follow an inverted U-shaped developmental trajectory with peak size occurring 1–3 years earlier in females compared to males. While 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.[20]

1.3 | The role of puberty versus 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.[21–24] In a functional MRI study of 105, 8–19 year olds, Ravindranath et al. found that while 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 while 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.[22]

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[22,25–27] 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.[4,15,28–33] The male and female brain develops differently during adolescence both in terms of structural connectivity and developmental trajectory.

Completely reversible neuropsychological effects would not be predicted given our current understanding of the 'windows of opportunity' model of neurodevelopment. If neuropsychological deficits associated with puberty blockers were completely reversible, it would mean that puberty is very different from the other pre-programmed windows of opportunity in neuropsychological development and any literature supporting this would present a significant challenge to our current understanding of neurodevelopment. It was the apparent incongruity between claims of full reversibility in the TDG literature and the neuropsychological puberty literature that prompted this review.

2 | LITERATURE REVIEW

2.1 | Methods

2.1.1 | 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 in the initial search. 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 measures of cognitive, neurobehavioural or neuropsychological function assessed on standardised tests and 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.

Since the focus of the review was on neuropsychological function, papers were included if they reported any quantified measure of cognitive function assessed on standardised neuropsychological measures or psychometric tests (or the equivalent in animal studies). Papers that reported outcomes measured via questionnaires or checklists (in humans) or self-reported measures of function were

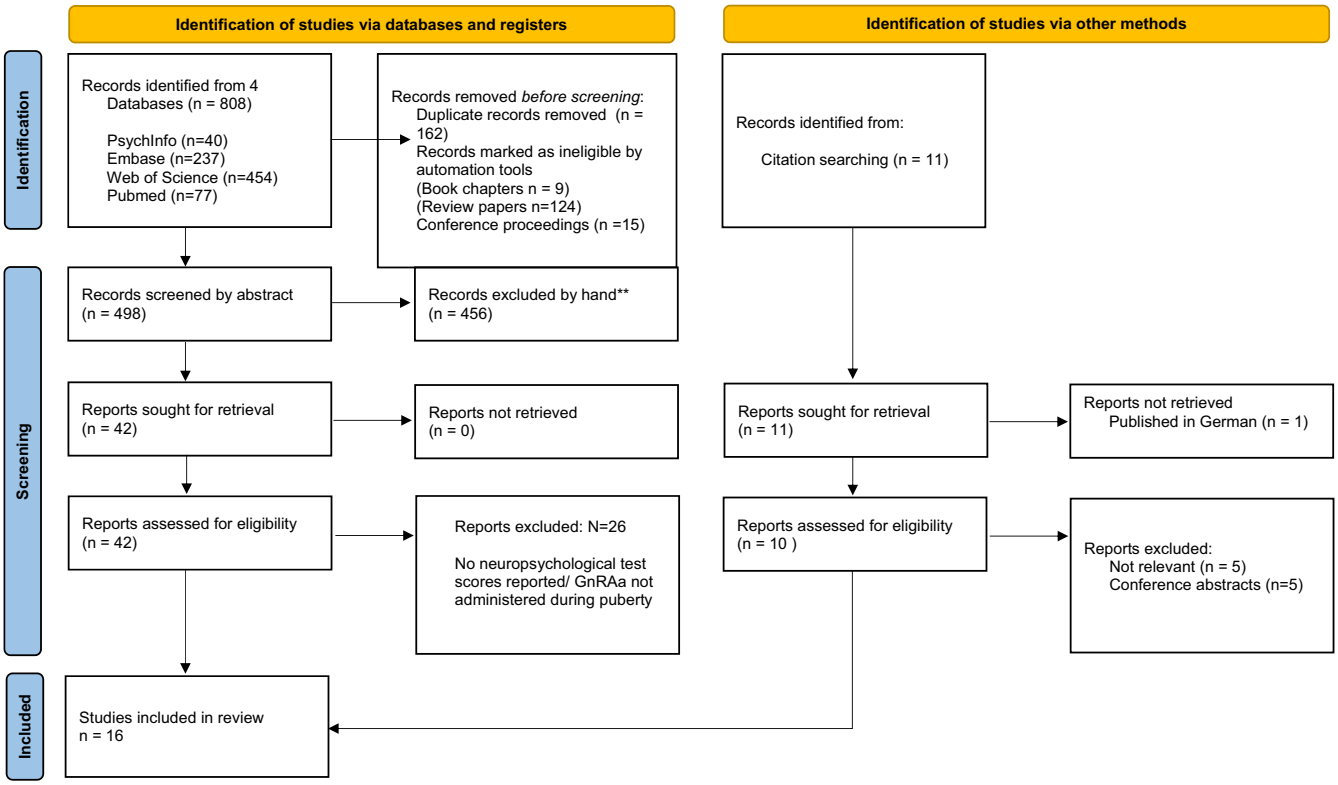

FIGURE 1 PRISMA flow diagram for systematic reviews which included searches of databases, registers and other sources: Search terms: GnRH*' or 'Lupron' AND 'Pubert*' and any of the following Neuropsychological Terms: Cogniti*, OR Neuropsychol*, OR 'Executive', OR 'Language', OR 'Memory', OR 'Learning', OR 'Spatial', OR 'Intelligence', OR 'IQ', OR 'Processing', OR 'Attention', OR 'Social'.

excluded. Papers that described psychological, psychosocial or psychiatric outcomes were also excluded.

3 | RESULTS

A number of relevant studies have been presented at conferences but have not subsequently been published in peer-reviewed journal articles. Sixteen peer-reviewed studies that have examined the impact of suppressing puberty with GnRH analogues on cognitive, neurobehavioral (animals) or neuropsychological function were identified with the search strategy described. The majority of these studies ($n = 11$) have been conducted in animals.

3.1 | Animal studies

The wider search strategy identified experimental studies on the physiological impacts of GnRH blockade 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 1. The majority of these studies ($n = 8$) have been conducted in the same flock of sheep using twin controls.[7,8,34–39] Two studies in monkeys[40,41] and one mouse study[42] were also identified. Measures of brain structure were reported in five 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 a GnRH antagonist/agonist has a detrimental impact on learning and the development of social behaviours and responses to stress in mammals.[7,8,34–36,38,39,41,42] Sex-specific effects were observed in multiple studies.[8,37,42] In male sheep, impairments in spatial memory associated with the treatment were not fully reversed following discontinuation of treatment.[39] Significant effects of treatment were also evident on measures of brain structure including overall volume,[41] functional connectivity[40] and neuronal density.[42]

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

TABLE 1 Animal studies examining the impact of GnRHa treatment on neuropsychological function or brain–behaviour relationships.

		Animal Model	Study design	Behavioural/cognitive domain assessed	Structural brain analyses	Main finding
1	Wojnius et al. (2011)	Male & female sheep	*N* = 48 same sex twin pairs GnRHa treated group (twin 1) vs. untreated controls (twin 2)	Food acquisition task	n/a	Results: Significant sex vs. treatment effects Treated males were more likely to leave their companions to acquire food than untreated males, while the opposite effect was observed in females Conclusion: Long-term prepubertal GnRHa treatment significantly affected sex-specific brain development, which impacted emotion and behaviour regulation in sheep. These results suggest that GnRH is a modulator of cognitive function in the developing brain and that the sexes are differentially affected by GnRH modulation
2	Evans et al. (2012)	Male & female sheep	*N* = 46 same sex twin pairs GnRHa treated group (twin 1) vs. untreated controls (twin 2)	Vocalisation Response to social isolation Tested at 8, 28 and 40 weeks	n/a	Results: Response to social isolation and vocalisation was significantly higher in females than males at all ages Conclusion: Development of responses to social isolation is sexually dimorphic and cortisol dependant. Treatment with a GnRH agonist results in changes in age-dependent development of this social function
3	Nuruddin et al. (2013)	Male & female sheep	*N* = 30 same sex twin pairs (14 female/16 male) GnRHa treated group (twin 1) vs. untreated controls (twin 2)	Test of spatial orientation 48 weeks of age	Hippocampal gene expression	Results: GnRHa treatment was associated with significant changes within the hippocampus, of levels of expression of mRNA transcripts known to be involved in endocrine signalling and synaptic plasticity. Expression of 12 out of the 16 genes was altered in GnRHa treated sheep compared to controls. These changes were not related to performance on a spatial maze test. Although there were no significant effects of treatment on performance in spatial maze, in males, there was a tendency that T animals were slower in completing the spatial maze than the controls during every trial. The author speculate that treated males might have been less motivated than control males to complete the maze in fastest possible manner Conclusion: GnRH1 mRNA expression in females might be more sensitive to GnRHa treatment
4	Nuruddin et al. (2013)	Male and female sheep	41 brains of sheep from the experiment described above 17 treated (10 females, 7 males) 24 controls (11 females, 13 males)	n/a	MRI volumes 1. Total brain 2. Amygdala 3. Hippocampus	Results: Highly significant GnRHa treatment effects were found in the volume of the right and left amygdala in treated animals, with larger amygdale in treated animals. Significant sex differences were found for total grey matter and right amygdala with larger volumes in males Conclusions: The effects of GnRHa treatment on amygdala volumes indicate that increasing GnRH concentrations during puberty may have an impact on normal brain development in mammals
5	Wojniusz et al. (2013)	Male and female Sheep	*N* = 46 twin pairs GnRHa treated group (twin 1) vs. untreated controls (twin 2)	Spatial orientation maze task 8 weeks 28 weeks 48 weeks	n/a	Results: GnRHa treatment did not affect spatial maze performance. No significant differences in traverse time between treated and untreated animals were observed at any time point prior to or following treatment. Adolescent females (48 weeks) outperformed the males in both groups Conclsuions: Development of sex differences in spatial orientation is independent from exposure to pubertal hormones

		Animal Model	Study design	Behavioural/cognitive domain assessed	Structural brain analyses	Main finding
6	Hough et al. (2017a)	Male Sheep	Group 1. GnRH and testosterone blocked $n=49$ Group 2. GnRH blocked, with testosterone replacement $n=22$ Group 3: Controls $n=56$	Spatial maze task 1. Traverse time 2. Long-term memory 3. Emotional reactivity 8 weeks 27 weeks 41 weeks	n/a	Results: Emotional reactivity was compromised by blockade of testosterone signalling, but was restored in the testosterone replacement group. The blockade of GnRH signalling alone was associated with impaired retention of long-term spatial memory and this effect was not restored with the replacement of testosterone signalling. The GnRHa + T group required fewer training sessions than the GnRHa group Conclusion: These results indicate that GnRH signalling is involved in the retention and recollection of spatial information, potentially via alterations to spatial reference memory. Therapeutic medical treatments using chronic GnRHa may have effects on this aspect of cognitive function
7	Hough et al. (2017b)	Male Sheep (as above)	Group 1. GnRHa treated until 44 weeks of age $n=25$ (Twin 1) Group 2. Controls $n=30$ (Twin 2)	Spatial memory task (as above) 83 weeks 95 weeks	n/a	Results: The long-term spatial memory performance of GnRHa-Recovery rams remained reduced ($p<0.05$, 1.5-fold slower) after discontinuation of GnRHa, compared to controls Conclusions: The time at which puberty normally occurs may represent a critical period of hippocampal plasticity. Perturbing normal hippocampal formation in this peripubertal period may also have long-lasting effects on other brain areas and aspects of cognitive function
8	Hough et al. (2019)	Male Sheep	Group 1. GnRH and testosterone blocked ($n=55$) Group 2. GnRH blocked, with testosterone replacement ($n=24$) Group 3: Controls $n=60$	Preference for novel vs. familiar objects Approach/avoidance behaviours Emotional reactivity 8 weeks 28 weeks 46 weeks	n/a	Results: Specific suppression of testosterone during a developmental window in late puberty may reduce emotional reactivity and hamper learning a flexible adjustment to environmental change Conclusion: Disruption of either endogenous testosterone signalling or a synergistic action between GnRH and testosterone signalling, may delay maturation of cognitive processes (e.g. information processing) that affects the motivation of rams to approach and avoid objects
9	Anacker et al. (2021)	Male and female mice	Control vs. GnRA injected mice	Locomotion Social preference Hyponeophagia Forced swim test	Brain immunohistochemistry	Results: *Sex-specific effects*: Males: GnRHa treatment altered locomotion and social preference and increased the corticosterone response to novelty exposure in the male but not female mice, Females. Treatment was associated with increased hypnoneophagia and despair-like behaviour and neural activity in the dentate gyrus in female mice without an effect in male mice. No treatment effects were observed on measures of avoidance behaviour or contextual fear discrimination in either sex Conclusion: GnRHa treatment is associated with sex-specific effects on measures of social and affective behaviour, stress regulation and neural activity

		Animal Model	Study design	Behavioural/cognitive domain assessed	Structural brain analyses	Main finding
10	Pincus et al. (2021)	Female Macaque Monkeys	GnRHa treated $n = 34$ Controls $n = 36$	Indices of social rank and social behaviour Responses to the human intruder task Tested at 43–46 months of age	Resting state MRI and T1 images	Results: GnRHa treated monkeys were more submissive and less affiliative than controls. They were less anxious and exhibited less displacement activity in the human intruder task Imaging revealed stronger functional connectivity between the left amygdala and left orbital frontal cortex in the treated group compared to controls Conclusion: Delayed puberty and subordination stress had separable effects, suggesting that the overlapping socioemotional outcomes may be mediated by distinct neuroplastic mechanisms
11	Godfrey et al. (2023)	Rhesus Macque monkeys	GnRHa treated $N = 23$ Controls $n = 22$	Measures of emotionality Response to acute stress	Structural MRI	Results: Treated animals differed from controls in intracranial volume (control volume < treated volume) however, hippocampal volume was larger in controls Conclusion: There are region-specific effects of Estradiol on structural brain development during adolescence

impacts are complex and often sex specific, consistent with the MRI evidence of sex-specific differences in neurodevelopment in human adolescence.[20] There is no evidence in the animal literature that these effects are reversible following discontinuation of treatment.

3.2 | Human studies

The search strategy identified just five studies that have reported some aspect of neuropsychological function following the administration of medications to suppress puberty in young people. Two studies reported the impact of treatment with a puberty blocker 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.

3.3 | Central precocious puberty

In the only human study that established a baseline prior to treatment, Mul et al.[43] examined the response to treatment with puberty blockers 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 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. While 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.[44] While 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.

The Wechsler Intelligence Scales are well designed to measure the impact of treatments on IQ in children. The norms are very robust and are provided for children at 3-month intervals, from age 6 to 17 years. Different abilities develop at different times and at different rates but at any point during their development, a child's scores on the tests that comprise the IQ battery can be compared to that of their age-matched peers. In order to maintain a stable IQ, the child will need to keep pace with the development of that seen in their peers. Of course, some children are very able, others less so. But the key characteristic of IQ is that it should remain stable throughout a child's development. Regardless of whether an individual performs at the 10th, 50th or 90th percentile when they are 8, they should continue to do so when they are 16. Any loss of IQ associated with treatment with puberty blockers indicates that the child's cognitive development is not keeping pace with that of his/her peers.

The Galatzer et al.[46] and Ehrhardt et al.[47] studies did not report the impact of puberty blockers on IQ but rather reported the IQ of girls with CPP. It is noteworthy that only three 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% vs 25%), and five times more in the very superior area (greater than 130, 10.1% vs 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.[45] 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 did not control for multiple comparisons (over 40) and that the groups did not 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 (studies from Galatzer et al. and Ehrhardt et al.),[46,47] the IQ in their CCP group was somewhat lower than the controls, although the difference was not statistically significant.

Wojniusz et al. state '*both groups (CPP and controls) showed* ***very similar*** (my emphasis) *scores with regard to cognitive performance*'.[45] 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 overemphasising 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 centile.[48]

3.4 | GnRH analogues and transgender and gender diverse young people

Three studies were identified that examined the neuropsychological impact of GnRH analogue treatments 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.[49] (See Figure 2).

In a cross-sectional design, Staphorsius et al.[50] 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 strategise). 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). While 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[44] and in policy documents.[51]

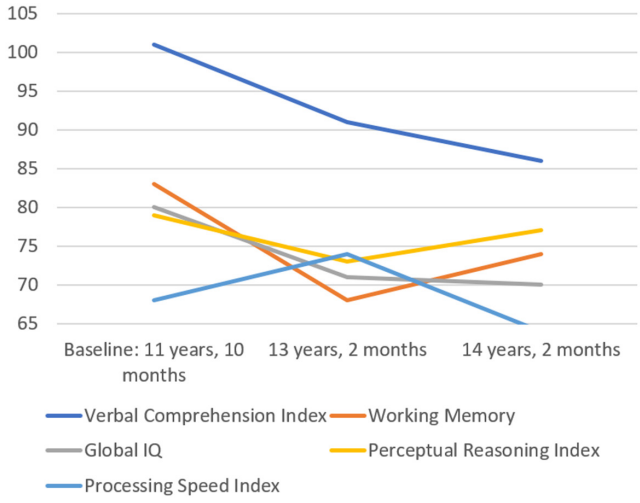

FIGURE 2 Longitudinal IQ scores following pubertal suppression in a single case study (adapted from Schneider et al.[49]).

Arnoldussen et al.[52] 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 per cent 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.

4 | 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,[46] 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.

While 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.[43,48,49] These findings accord 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. While 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.[51,53] Indeed, the only study to date that has addressed this in sheep suggests that this is not the case.[39]

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[19,34,42] consistent with imaging studies in adolescents which indicate different trajectories of neurodevelopment in males and females.[20] 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,[54] 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.[55,56] Neurodiversity is overrepresented in TGD people, who are three to six times more likely to have a diagnosis of autism than their peers.[55] 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.[56] 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[57] 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.[58] 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.[59] 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.[60] 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 neuropsychological 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. While 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. 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. 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.

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Sallie Baxendale: Conceptualization; data curation; formal analysis; visualization; writing – original draft; methodology; investigation; project administration; writing – review and editing.

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