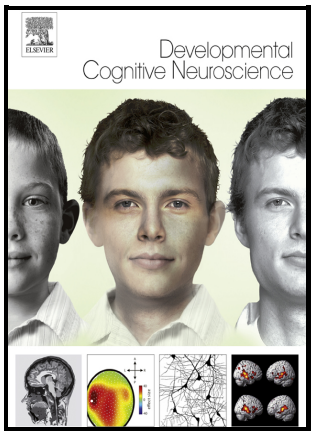

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Adolescent neurocognitive development and decision-making abilities regarding gender-affirming care

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Abstract

Recently, politicians and legislative bodies have cited neurodevelopmental literature to argue that brain immaturity undermines decision-making regarding gender-affirming care (GAC) in youth. Here, we review this literature as it applies to adolescents' ability to make decisions regarding GAC. The research shows that while adolescence is a time of peak risk-taking behavior that may lead to impulsive decisions, neurocognitive systems supporting adult-level decisions are available given deliberative processes that minimize influence of short-term rewards and peers. Since GAC decisions occur over an extended period and with support from adult caregivers and

clinicians, adolescents can engage adult-level decision-making in this context. We also weigh the benefits of providing GAC access during adolescence and consider the significant costs of blocking or delaying GAC. Transgender and non-binary (TNB) adolescents face significant mental health challenges, many of which are mitigated by GAC access. Further, initiating the GAC process during adolescence, which we define as beginning at pubertal onset, leads to better long-term mental health outcomes than waiting until adulthood. Taken together, existing research indicates that adolescents can make informed decisions regarding gender-affirming care, and that this care is critical for the well-being of TNB youth. We highlight relevant considerations for policy makers, researchers, and clinicians.

Keywords: adolescence, gender-affirming care, transgender, cognition, decision-making, policy

1. Introduction

Literature on neurocognitive development has recently been interpreted to suggest that due to protracted maturation of key neurocognitive systems, adolescents cannot engage in complex cognitive processes, undermining their ability to understand the consequences of medical decisions such as in gender-affirming care (GAC). GAC encompasses a broad range of social, psychological, behavioral, and medical interventions that aim to "support and affirm an individual's gender identity" when it is misaligned with that assigned at birth (Boyle, 2022). In this paper, we primarily focus on the decision to initiate medical intervention, including puberty blockers and gender-affirming hormone therapy (GAHT), with less emphasis on social transition. Since 2021, the United States has introduced 25 bills (at the time of this paper) in state legislatures and 3 federal bills in the House of Representatives restricting access to GAC to transgender and non-binary (TNB) adolescents. This legislation has cited developmental cognitive neuroscience studies and interpreted them as reflecting limitations in the ability of adolescents and young adults to engage

brain systems underlying decision-making (Kraschel et al., 2022; Shutt et al., 2022). However, critically, this legislation has not integrated the broader understanding of decision-making capability in adolescence that is particularly relevant to GAC. Here we discuss the relevant adolescent neurocognitive research and clarify its implications for decision-making in GAC.

We also discuss the potentially devastating effects of restricting access to GAC in youth, particularly due to the increased vulnerability to psychiatric illness during adolescence (Paus et al., 2008). TNB youth are particularly vulnerable and experience up to 3 times higher rates of depression, anxiety, and suicidality as compared to their cisgender peers (Kuper et al., 2019; Moyer et al., 2019, p. 9; J. Olson et al., 2015; Strauss et al., 2020). A study in TNB adolescents and young adults at their first gender clinic visit found that 1 in 3 youth met diagnostic criteria for Major Depressive Disorder (MDD) and 1 in 2 met criteria for a diagnosis of Generalized Anxiety Disorder (GAD) (Chodzen et al., 2019). In addition to affective disorders (e.g., MDD, GAD), TNB youth are at significantly elevated risk for eating disorders (Connolly et al., 2016; Diemer et al., 2015) and problematic substance use (Day et al., 2017) as compared to cisgender youth.

Even more urgently, exorbitantly high levels of suicidality have been observed among TNB youth, with 29-50% of TNB youth reporting suicide attempts as compared to 10-18% of cisgender youth (Toomey et al., 2018), and 86% of TNB youth endorsing suicidality within the past 6 months (Austin et al., 2022). Even in comparison to their peers in the LGBQ+ community, TNB youth are at uniquely greater risk for suicidal ideation and suicide attempts (Johns et al., 2019; Price-Feeney et al., 2020; Toomey et al., 2018). Unfortunately, recent work suggests that this crisis is rapidly worsening, with increasing suicide rates among TNB youth driving an uptick in the percentage of LGBTQ+ Americans dying by suicide, increasing from 13% before November 2016 to 20% after

(Ream, 2022). Many TNB youth cite gender dysphoria, struggles with identity, and associated stigma as a primary cause of their mental health struggles (Grossman & D'Augelli, 2007).

While these findings may seem bleak, adolescence is a window of opportunity for mental health intervention, and research shows that providing TNB youth with comprehensive support to pursue GAC can mitigate long-term negative mental health outcomes (K. R. Olson et al., 2016). Therefore, legislation restricting access to GAC during adolescence and young adulthood may result in deleterious outcomes for TNB youth. Importantly, though many proponents of these restrictions claim that youth may regret their GAC decisions later in life, research has shown that "transition regret" is rare (Brik et al., 2020; de Vries & Cohen-Kettenis, 2012; Narayan et al., 2021), with large studies estimating rates of regret at 1% or less (Bustos et al., 2021; Wiepjes et al., 2018).

This review aims to summarize the existing literature to provide critical context to professionals working within legal, political, and legislative spaces pertaining to juvenile GAC decisions, in addition to clinicians working with TNB youth and scientists conducting research in this area. We first summarize relevant adolescent neurodevelopmental literature regarding cognition, including decision-making, followed by clarification of key findings that have been misinterpreted and incorrectly applied to justify the passage of bills restricting TNB youth from access to GAC. Finally, we expand on why denying GAC to adolescents is likely to exacerbate an already critical mental health crisis among TNB youth.

2. Cognitive Control in Adolescence

Adolescence, defined in this paper as the onset of puberty, is a time of significant refinement of brain mechanisms underlying social, emotional, and cognitive development that will determine adult trajectories. Developmental improvements in executive function and top-down

cognitive control occur in parallel with brain maturation as the integration of distributed neural circuitry strengthens, stabilizing around 18 years of age (Blakemore, 2012; Kundu et al., 2018; Luna et al., 2004; Marek et al., 2015; Nadig et al., 2021; Tervo-Clemmens et al., 2022). However, as we discuss below, adolescence is marked by variability in adult-level executive systems. While adolescents may engage these executive abilities inconsistently, which can lead to impulsive decision making in certain contexts, they can be readily engaged when given time to deliberate and carefully consider options. The field's current understanding of adolescent neurocognitive development indicates that adolescents and young adults can make adult level, goal-oriented decisions, including those with long term consequences, provided the appropriate context – which includes support from adults, longer timescales, and information required to evaluate the outcomes (Fig. 1). Thus, arguments by legislators restricting GAC access for TNB youth on the grounds that the executive brain system is not yet "fully developed", rendering adolescent and young adult decisions uninformed and possibly non-consensual, contradict evidence from developmental cognitive neuroscience. Here, we summarize the current relevant knowledge regarding brain development during adolescence, and present evidence that the GAC process provides a context in which adolescents and young adults can engage executive systems at an adult level to make informed and thoughtful choices regarding their own medical care.

2.1 Neurobiological Mechanisms Underlying Cognitive Development Through Adolescence

Cognitive control is the ability to engage executive function to support deliberative goal-directed responses. These abilities are present in a rudimentary form from infancy followed by rapid improvements in the ability to engage these systems in a controlled and consistent manner across development (Amso & Johnson, 2005; Diamond & Goldman-Rakic, 1989; Johnson, 1995). This maturation is supported by reliable access to prefrontal cortical systems and relevant brain

networks. Laboratory tasks assessing cognitive control have shown that by adolescence, prefrontal systems can be engaged in a similar manner as adults, albeit at a lower rate and with greater variability (Montez et al., 2017; Ordaz et al., 2013; Simmonds et al., 2014). Brain maturation through adolescence that supports cognitive control includes thinning of gray matter across cortical and subcortical regions (Gogtay et al., 2004), pruning of excess synapses in the prefrontal cortex (Petanjek et al., 2011), and increased myelination in tracts linking association cortices to other regions critical for cognitive processing (Asato et al., 2010; Lebel et al., 2008; Simmonds et al., 2014; Yakovlev et al., 1967). These maturational changes are evident in the decreasing communication between core executive prefrontal and reward striatal regions into adulthood, reflecting dampening of reward-driven influence on cognitive control (Parr et al., 2021, 2022). Further, more recent work has suggested that adolescence may be a critical period of neurodevelopment in executive prefrontal cortex when excitatory glutamatergic and inhibitory GABAergic neurotransmitter signals in the brain become increasingly balanced, supporting reliable brain functioning in early adulthood (Larsen & Luna, 2018; Perica et al., 2022). Taken together, these neurobiological changes support the specialization of neural systems and greater reliability of cognitive performance, both of which are known to underlie brain maturation throughout adolescence and into adulthood (Honkanen et al., 2015; Katz & Shatz, 1996; Lewis et al., 2004; Marek et al., 2015; Scholl et al., 2015; Toyoizumi et al., 2013).

In line with this neuroimaging evidence, behavioral studies have also characterized the age of transition to adult-level cognitive control. Several studies have shown that adult-level cognition is fully established by age 18, including a recent study leveraging a multi-site, longitudinal combined sample of over 10,000 participants ages 8-35 (Ferrer & McArdle, 2004; McArdle et al., 2002; Tervo-Clemmens et al., 2022). However, as previously mentioned, even adolescents

younger than 18 can engage neurobiological systems supporting executive functioning in an adult-like manner, albeit inconsistently. Through late adolescence, the ability to engage these systems reliably improves, as evidenced by decreased intrasubject variability into young adulthood (Montez et al., 2017). Thus, given sufficient opportunities to engage these executive systems, adolescents can demonstrate adult-like performance. Furthermore, the finding of adolescents reaching adult-like levels of executive functioning at 18 years old represents a group average, which obscures meaningful individual differences in developmental trajectories of cognition. Thus, these cognitive abilities may mature earlier in some adolescents and later in others (Foulkes & Blakemore, 2018), a critical consideration in the discussion of the ability for adolescents to make decisions regarding their medical care. Indeed, the recently published World Professional Association for Transgender Healthcare (Version 8) has argued for a personalized approach to assessing readiness for GAC in adolescents, with consideration of the individual's pubertal maturation, cognitive, social, and emotional development, and other environmental factors (Coleman et al., 2022).

2.2 Adolescent Decision Making & GAC

Although cognitive systems are in place by adolescence, the continued refinement of inhibitory control coupled with an increase in motivational drive gives rise to normative increases in impulsive, reward-driven, and sensation-seeking behaviors (Spear, 2000), oft-cited hallmark characteristics of adolescents (Shulman et al., 2016). These behaviors are adaptive and motivate the acquisition of novel experiences required to meet environmental demands (Hartley & Somerville, 2015; Larsen & Luna, 2018; Spear, 2000). However, these adaptive increases in reward- and sensation-seeking can also lead to risk-taking behaviors that are exacerbated in the presence of peers and can increase mortality (Fig. 1; e.g., reckless driving, substance use initiation,

see Shulman et al., 2016 for review). A large body of neurobiological research has shown that adolescent increases in impulsive behaviors and risk-taking are associated with asynchronous maturation of striatal reward systems and executive prefrontal systems (Fig. 1; (Shulman et al., 2016).

Inhibitory control—the ability to suppress an impulsive response—undergoes significant maturation during adolescence (Luna et al., 2004). This ability is available in adolescence, although it can be variable, and in certain contexts, is driven toward obtaining immediate reward (Luna & Wright, 2016). Neurodevelopmental models, including the Driven Dual Systems model (Fig. 1; (Luna & Wright, 2016; Shulman et al., 2016) suggest a relative predominance of reward (i.e., striatum) and affective (i.e., amygdala) systems over newly matured prefrontal cognitive control systems (responsible for planning and deliberation) that bias decision-making towards reward in early and mid-adolescence (Luna & Wright, 2016). Evidence shows that functional coupling between executive prefrontal systems and striatal reward systems decreases into young adulthood (Fareri et al., 2015; Parr et al., 2021; van Duijvenvoorde et al., 2019) in parallel with reward system integration (Murty et al., 2018) and stabilization of dopamine function, the neurotransmitter that supports reward processing (Andersen et al., 1997; Larsen et al., 2020; Luciana et al., 2012; Parr et al., 2021, 2022; Wahlstrom et al., 2010). These changes have been found to be associated with developmental decreases in reward-driven behaviors (Galvan et al., 2006; Luciana et al., 2012; Parr et al., 2022).

Although adaptive, the adolescent propensity for immediate rewards can lead to risky decision-making in certain contexts, which can result in deleterious consequences (Steinberg, 2004). When required to make decisions within a short timescale, especially in the context of heightened emotion (“hot” contexts; Fig. 1), adolescents have been shown to be driven by short-

term rewards (i.e., monetary incentives) rather than considering long-term outcomes. Further, when decisions are made quickly (i.e., impulsively), the consequences of an individual's actions may be ambiguous, particularly for adolescents (Hartley & Somerville, 2015). Impulsive decision-making during adolescence in these "hot" contexts can also be exacerbated in the presence of peers (Chein et al., 2011; O'Brien et al., 2011; Smith et al., 2014; Weigard et al., 2014). Indeed, adolescent impulsive risk-taking behavior decreases when decisions are made outside of social contexts. For example, while adolescents demonstrate adult-level decision-making when performing a driving simulation alone or with an adult, they engage in more risky behaviors when in the presence of peers (Chein et al., 2011; Guassi Moreira & Telzer, 2018; Simons-Morton et al., 2011). These results demonstrate that adolescents can make adult-level, safe, and responsible decisions given ideal circumstances (i.e., in the presence of adults in "cold" contexts, outside of "hot" contexts). Considering this, legislative bodies have employed these findings to inform laws promoting more favorable circumstances for adolescents in potentially "hot" contexts, such as driving laws requiring adolescents possessing a "learner's permit" to be in the presence of a licensed adult (Cohen et al., 2016). Importantly, this body of neurodevelopmental research has been used to inform American Medical Association US supreme court briefs, citing work showing that the adolescent peak in reward-driven reactive behaviors should be considered when determining adolescent culpability (Cohen et al., 2016). This has resulted in an overturn of the juvenile death penalty (*Graham v. Florida*, 2010; *Miller v. Alabama*, 2012; *Roper v. Simmonds*, 2004; Jones et al., 2014) and has been considered by several legal briefs regarding culpability assessments in juvenile sentencing (Cohen et al., 2016). This legal precedent (and findings on adolescent brain development more generally) is now being applied by various state lawmakers to suggest that adolescents cannot make competent medical decisions regarding GAC. However, as

has been noted by Cohen et al., (2016), critical differences exist between these "hot" decisions that are the subject of legislation concerning youth offender sentencing, and decisions made in contexts concerning medical decisions, including GAC (Steinberg et al., 2013). Below, we argue that decisions regarding GAC cannot be made impulsively, as they occur over a protracted timescale, are deliberative, involve adult support, and engage different neurocognitive processes from what is typically characterized as "impulsive" decision-making.

In contrast to "hot" impulsive, risk-taking behaviors, research has shown that adolescents (at approximately 15-16 years of age) can engage cognitive control capabilities at adult-like levels when decisions are made under "cold" contexts (Fig. 1) – that is, without the pressure to decide quickly, when peer influence is minimized, resulting in less engagement of the reward- and affective system (Byrnes, 2002; Figner et al., 2009; Icenogle & Cauffman, 2021; Wolff & Crockett, 2011). These "cold" contexts facilitate more thoughtful planning, deliberation, and the ability to reflect on and simulate the potential costs and benefits of their decisions, thus reducing the level of uncertainty inherent to decisions often made in "hot" contexts (Icenogle & Cauffman, 2021; Nigg, 2017). To return to the Dual Systems Model, cognitive control processes may predominate over affective systems when not in a state of heightened reward or peer stimulation, facilitating deliberative decisions akin to those made by adults (Icenogle & Cauffman, 2021). Thus, while adolescents and adults differ in contexts that preclude deliberation via high reward and/or emotional arousal, the decision-making process in situations that encourage deliberation and reflection is similar among adolescents and adults.

Medical decisions, including GAC, are typically made under "cold" contexts, and occur over a long period of time (Steinberg et al., 2013). The process of scheduling a GAC intake/consultation appointment can take months to years, with several built-in "off ramps" during

which adolescents can consider alternative therapeutic approaches. Furthermore, adolescents are often aware of their gender identities for years prior to disclosing this information to others (i.e., family members, peers), and prior to making the decision to seek GAC (Bauer et al., 2022; Haimson & Veinot, 2020; Scandurra et al., 2021), and in many situations, may have already 'socially transitioned'. Therefore, while many are concerned that adolescents are making GAC decisions impulsively, the context of GAC involves long periods of time and deliberation. In fact, timely access to GAC likely presents a much larger concern, with wait times ranging from 1 to 5 years in Europe (Ellis et al., 2015; Pullen Sansfaçon et al., 2019; Ross et al., 2023) and several months to up to 7 years in the United States and Canada (El-Hadi et al., 2018). These extended wait times, along with other barriers to care such as the limited number of GAC providers and health insurance coverage limitations (Pullen Sansfaçon et al., 2019), increase the timescale for obtaining GAC far beyond that necessary to support deliberative decision-making (Imbler, 2021; Savage & Bauer, 2021). Furthermore, while risky behavior exacerbated by the presence of peers occurs predominantly in "hot" situations, GAC decisions are made with substantial support from adult caregivers and/or medical professionals. These decisions entail numerous discussions that are highly future-oriented, well-informed, and made in the presence of adults, facilitating a supportive environment conducive to informed decision-making (Fig. 1; (Grootens-Wiegers et al., 2017). In fact, evidence suggests that adolescents as young as 12 years old possess the capacity to participate in medical decisions based on four factors: communicating their choice, understanding the information provided about the proposed medical treatment, reasoning (deliberating the risks and benefits), and appreciation of both the options and the personal consequences of their decision (Grootens-Wiegers et al., 2017). In contexts with similar dynamics, adolescents have been shown to be capable of complex cognition and judgement required to make decisions regarding their own

care and lifestyle, including obtaining and maintaining employment, participating in school, and planning for future scholarly pursuits, and specifically in medical contexts, informed treatment consent (Weithorn and Campbell, 1982; Grisso and Vierling, 1978). Taken together, the neurodevelopmental literature indicates that adolescents possess the neurocognitive maturity to make long-term decisions, including decisions regarding GAC, given previously described 'cold' contexts and adequate time for deliberation.

Importantly, arguments by legislatures enacting restrictions to GAC access have been made on the basis of the observation that there are elevated rates of psychiatric illness among TNB youth that may impact decision-making capabilities, which may need to be resolved prior to the initiation of GAC. However, symptoms of depression, anxiety, and suicidal ideation that are most prevalent in TNB youth primarily impact "hot" decision-making processes, including reward and affective (emotional) processes (Forbes & Dahl, 2012; Hardin et al., 2007; Mukherjee et al., 2020), which do not characterize the decision process underlying GAC. The systems required for deliberative, future-oriented, decisions ("cold" decision-making), that are made with the support of adults, have not been shown to be impacted in the same manner by anxiety and depression symptoms, mitigating concerns regarding their impact on adolescents' decision to pursue GAC. In addition to these findings, and in part on the basis of these findings, the World Professional Association for Transgender Health Standards of Care (Coleman et al., 2022) does not recommend ameliorating mental health concerns as a condition of initiating GAC, except when mental health symptoms may affect capacity to consent to treatment or interfere with care adherence following treatment (i.e., post-surgical care).

2.3 The Neurobiology of Adolescent Social Development & its Association with GAC

Related to the idea of engaging in "impulsive decision-making" is the widely appreciated observation that adolescents are particularly susceptible to social pressures, such as those from peers, which may contribute to engagement in more risk-taking behaviors as previously stated. Social factors, such as input, support, or pressure from peers, are therefore thought to play an outsized role in adolescent decision-making compared to other age groups (Albert et al., 2013; Rosen et al., 2018; Steinberg, 2005) due to the increased salience of social stimuli and rewards during this time (Somerville, 2013). Across adolescence, socioemotional circuitry becomes specialized (Vijayakumar et al., 2018), developing in conjunction with pubertal processes (Dahl et al., 2018; Gardner & Steinberg, 2005; Ladouceur, 2012) and ongoing cognitive maturation, to support adolescent navigation through increasingly complex social hierarchies and peer relations while distinguishing an individual's self-identity in relation to others (Blakemore, 2012; Pfeifer & Allen, 2021). Much of the work examining social influences on decision-making has focused on dangerous risk-taking behaviors in the presence of peers (e.g., reckless driving, substance use, delinquency) (Pfeifer et al., 2011; Steinberg, 2008). However, as discussed above, these “hot” situations typically involve valuing short-term rewards (e.g., peer approval) over long-term consequences (e.g., dangers posed to one’s safety) (Beyth-Marom et al., 1993). Thus, this research cannot be applied to the context of decision-making regarding GAC, which is necessarily a long-term, deliberative process that is substantially supported by adults rather than simply influenced by peers.

Relatedly, many calls for bans on GAC for youth have cited this work on social development and decision making in adolescence, suggesting that “trans identity” is part of a “social contagion” (Littman, 2018). This claim was inspired by work that did not include TNB youth in their sample, but rather, sampled parents of TNB youth recruited from websites concerned

with “Rapid-Onset Gender Dysphoria,” which is not a clinical diagnosis (Littman, 2018). This study was strongly disputed by later work (Bauer et al., 2022; Turban, Dolotina, et al., 2022) and critiques have since noted several critical flaws in the Littman study, such as the use of a highly biased convenience sample and the lack of measure reliability or validity (Restar, 2020). Proponents of the “social contagion” theory purport that due to adolescents’ vulnerability to social pressures, their decisions may simply echo trans-supportive narratives or reflect socially liberal environments. This, however, ignores the fact that peer influences are more likely to lead to victimization of TNB youth, rather than adoption of TNB identity (Hatchel & Marx, 2018). For example, youth who receive GAHT experience greater gender identity-based victimization than those who wanted but did not receive GAHT (Green et al., 2021). Importantly, not all social influences negatively impact TNB youths' mental health. Research indicates that strong social support networks are protective factors for psychopathology risk in TNB adolescents (Johns et al., 2019; Kia et al., 2021; Tankersley et al., 2021). Taken together, in contrast to oft-cited concerns emphasizing the outsized role of social pressures in GAC decision-making, social belongingness and supportive social structures are protective factors for TNB youth and the choice to pursue GAC is usually in spite of oppositional forces across academic, domestic, medical, and social domains.

2.4 Establishment of Gender Identities and the Choice to Transition

Within the context of ongoing cognitive development and increased salience of social stimuli, adolescents are immersed in the process of determining their own unique identities. An established and stable sense of self is believed to be one of the central tasks of adolescence (Erikson, 1968). Behavioral studies have shown individual differences in the speed and trajectory with which adolescents progress through stages of identity exploration and commitment

(Grotevant, 2016; Kerpelman et al., 1997; Meeus, 1996), which are associated with psychological well-being, self-reflection, social support, and social conflict (R. M. Jones et al., 2014; Kerpelman et al., 1997; Luyckx et al., 2008; Meeus et al., 1999). Critically, the known increase in brain plasticity during adolescence provides opportunities for identity exploration. Existing neuroimaging work on identity development has focused on the prefrontal cortex and ventral striatum due to their roles in self-referential processing and delayed gratification (Crone & Fuligni, 2020), and has shown associations between identity strength/uncertainty and gray matter volume in this network (Becht et al., 2018, 2020). Thus, several aspects of adolescent brain maturation may also underlie identity development.

While adolescence is a key period of overall identity formation, research has found that gender identities often develop prior to adolescence, although this development can also extend to later in life. A recent study observed that 81% of trans women and 80% of trans men reported their gender dysphoria as one of their earliest memories (mean ages: 6.71 and 6.17, respectively) (Zaliznyak et al., 2021). Separate work in 3–12-year-old TNB children found that gender identities in this sample emerged as early as ages 3-4, with no significant age differences between cisgender and transgender children (Gülgöz et al., 2019). However, a recent review paper highlighting the existing literature on the neurobiological underpinnings of gender identity (Levin et al., 2023) revealed that most research in this area has been conducted in populations seeking care from gender clinics, has not accounted for mental health disparities, and has included racially homogeneous samples, leading to bias in the results, which tend to be contradictory and misinterpreted by the public (Levin et al., 2023).

A related and often raised concern is that youth may regret their decision to pursue GAC since identities are still being established. However, transition "regret" is rare (de Vries & Cohen-

Kettenis, 2012; Narayan et al., 2021). One large study of 27,715 TNB individuals in the United States found that only 13.1% of youth who pursued gender affirmation (i.e., GAC) reported "detransitioning," or discontinuing some or all aspects of gender affirmation (Turban, Loo, et al., 2021). However, as the authors note, "detransitioning" has been incorrectly conflated with regret, as most of these individuals (82.5% of those who reported detransitioning) identified one or more "external" factors contributing to their decision, such as pressure from family, unsupportive school environments, and/or sexual assault (Turban, Loo, et al., 2021). A separate large-scale study in the Netherlands of TNB individuals, the majority of whom underwent gender reassignment surgery, similarly found regret to be rare, with 0.6% of trans women and 0.3% of trans men reported experiencing regret (Wiepjes et al., 2018). A meta-analysis across 27 studies (N= 7,928) similarly observed regret following gender-affirmation surgeries to be rare, with <1% and 1% of people undergoing trans masculine and trans feminine surgeries, respectively, reporting regret (Bustos et al., 2021). Moreover, for the small number of individuals who do experience regret related to GAC, many interventions provided during adolescence are reversible. Thus, arguments citing “regret” are not well supported by the extant literature and should therefore hold little, if any, weight when considering an adolescent’s choice to seek GAC.

3. Developmental Consequences of Psychopathology for TNB Youth in Adolescence

3.1 Neurodevelopmental Effects of Psychopathology

Across cultures, adolescence is a time of heightened risk for the emergence of psychiatric disorders, including depression, anxiety, and eating disorders, as well as suicidality (Paus et al., 2008). Developmental researchers have theorized that the emergence of these disorders may reflect deviations from normative neurodevelopmental trajectories (Marquand et al., 2019; Parkes et al., 2021). One contributing factor to this vulnerability is the onset of puberty, a defining feature of

adolescence in which hormonal surges lead to biological changes that prepare the body for reproduction and adulthood (Vijayakumar et al., 2018). While the mechanisms by which puberty relates to mental illness are still unclear, pubertal onset has been consistently associated with increased psychopathology (Angold et al., 1998; Ge et al., 2003; Kaltiala-Heino et al., 2001; Kaltiala-Heino, Kosunen, et al., 2003; Kaltiala-Heino, Marttunen, et al., 2003; Mendle et al., 2010), suggesting that puberty may contribute to the greater prevalence of psychiatric disorders during adolescence. The increased depression and anxiety associated with pubertal changes is particularly pronounced in TNB youth, for whom pubertal physical changes (i.e., breast development, facial hair growth, menses onset) can cause additional distress, as their bodies start to look and feel more incongruent with their gender identities (Riggs et al., 2020). As mentioned previously, these rates of mental illness are significantly higher in TNB youth than their cisgender counterparts, and TNB adolescents cite gender dysphoria as a primary cause of their psychological distress.

Given that adolescence may be a critical period of neurodevelopment, structural and functional alterations in neural systems resulting from psychopathology (Fitzgerald et al., 2008; Maron & Nutt, 2017) could have outsized consequences for mental health and neurodevelopmental trajectories. In adolescence, psychopathology has been associated with alterations in subcortical brain regions that are critical for affective function as well as memory and planning, including reductions in hippocampal volume (Whittle et al., 2013) and amygdala-hippocampal connectivity (Lichenstein et al., 2016). Further, reduced striatal activation for rewards has been observed in adolescents with depression compared to those without, particularly regarding social rewards (Forbes & Dahl, 2012). Psychiatric risk, including depression, anxiety and trauma-related disorders, has also been associated with alterations in frontal systems during adolescence (Beesdo

et al., 2009; Cisler & Herringa, 2021; Lichenstein et al., 2016; Miller et al., 2015). Particularly, research has shown that functional activation and functional connectivity of the anterior cingulate cortex, which is involved in many higher-order functions including error monitoring and emotion regulation (Botvinick et al., 1999), is impacted in adolescent depression (Lichenstein et al., 2016; Miller et al., 2015).

While minimal research has examined how adolescent mental illness affects adult neurocognitive outcomes, it has been shown that adolescent depression is associated with greater risk for depression recurrence, anxiety, and suicidality in adulthood (D. Johnson et al., 2018). Due to heightened brain plasticity during adolescence, recurrent maladaptive experiences during this period, such as episodes of psychiatric illness, could lead lasting impacts on the brain in adulthood. The high prevalence of these disorders in TNB youth puts them at increased risk for these long-term deleterious effects when they do not receive treatment, and even more so when they encounter a lack of support, discrimination, or stigma that may worsen these symptoms.

3.2 Impacts of Stress and Trauma across Development

Two multifaceted stressors—gender minority stress and gender dysphoria—are thought to underlie the emergence of psychopathology in TNB youth (Turban & Ehrensaft, 2018). Briefly, *gender minority stress* refers to external social stressors, such as stigma and discrimination (Hunter et al., 2021), that result from the marginalization of a minority gender identity in a cisnormative society (Tan et al., 2020). TNB minority stress stems from societal reinforcement of binary gender expectations, and the penalization or pathologization of gender non-conformity (Riggs et al., 2015; Riggs & Treharne, 2017; Tan et al., 2020). In contrast, *gender dysphoria* refers to internal distress related to one's body developing in a manner incongruent with one's gender identity (Dolotina & Turban, 2022). Common psychosocial stressors faced by TNB individuals, such as lack of safe

access to public facilities, housing and employment discrimination, and physical violence (Hendricks & Testa, 2012), contribute to both gender minority stress and gender dysphoria. One 2015 survey estimated that nearly 1 in 3 TNB youth in the U.S. were living in poverty, twice as many as their cisgender counterparts (James et al., 2016), and 35-39% of TNB youth report homelessness at some point in their lives (DeChants et al., 2022), due to family conflicts and/or abuse (Abramovich, 2016; Forge, 2018; Shelton & Bond, 2017).

Critically, stressful life experiences, such as those regularly experienced by TNB youth, are thought to impact neurodevelopment, thus putting individuals at increased risk for mental illness (Benjet et al., 2010; Kessler et al., 2018; Varese et al., 2012). Stress hormones, such as cortisol, can cross the blood-brain barrier, bind to receptors on neurons, and directly exert effects on neural activity (Banks, 2012; Joëls, 2018; Joëls & Baram, 2009; Raymond et al., 2018). Much of the work done thus far examining the impact of stress on brain development has focused on adversity experienced in childhood. The Stress Acceleration Hypothesis model proposes that stressful experiences in early life shift the developmental trajectories of neural systems, leading to premature development of emotional and associative learning systems (Callaghan & Tottenham, 2016). While this confers advantage for responding to stress and threats, it has the disadvantage of shortening the potential window of adaptive prefrontal plasticity. Additional work has shown that stress in early life can impact brain structure, particularly in brain regions such as prefrontal cortex and hippocampus that are involved in higher-order functions such as executive function and emotion regulation (Hanson et al., 2012; P & Da, 2011). More recently, studies have built on this work by investigating the impacts of stress on brain development when stressful life experiences occur during adolescence (Perica & Luna, 2023). It is critical to examine these changes during adolescence due to normative development of the stress response system, demonstrated by

increases in the stress hormone cortisol, that could predispose adolescents to heightened stress responses (Shirtcliff et al., 2012). This heightened stress reactivity interacting with ongoing neurodevelopmental processes may allow stress to sculpt neural circuitry during adolescence more so than in other developmental periods (Edmiston et al., 2011). Further, there may be specific interactions between cortisol and pubertal hormones that could uniquely impact adolescent trajectories, such as the potential role of cortisol in modulating the association between pubertal hormones and mood (Chronister et al., 2021; Mehta & Prasad, 2015). In addition, chronic stress exposure and long-term stress hormone production may lead to changes in the production of pubertal hormones that have opposing effects to cortisol (Kamin & Kertes, 2017). Thus, stress experienced during adolescence could have a major impact on prefrontal development due to heightened plasticity in prefrontal cortex (Lupien et al., 2009), as well as interactions with ongoing pubertal development, thereby affecting eventual adult outcomes.

4. GAC Mitigates Mental Health Risks

Although TNB individuals are at elevated risk for psychopathology and stress susceptibility, receiving GAC during adolescence appears to reduce this risk. Thus, adolescence may represent a window of opportunity during which empirically-based intervention can promote healthy development. Studies in TNB youth have found associations between receiving GAHT and lower risk for depression and suicidality (Green et al., 2022; Tordoff et al., 2022). Furthermore, a large study in the United States (N=22,715), receiving GAHT during either adolescence or adulthood was associated with less suicidal ideation compared to those unable to receive GAHT (Turban, King, et al., 2022). Studies using this dataset showed that receiving GAHT in adolescence was associated with better psychological outcomes and a lower risk of suicidal ideation than receiving GAHT during adulthood, and significantly lower rates of lifetime suicidal

ideation in trans adults who wanted and received pubertal blockers during adolescence, compared to those who were denied pubertal blockers (Turban et al., 2020; Turban, King, et al., 2022). These findings suggest that receiving GAC during the adolescent neurodevelopmental period significantly reduces the risk of severe psychopathology during adolescence and across adulthood.

Taken together, individuals receiving GAHT during adolescence have markedly better mental health outcomes, compared to those who must wait for GAHT until adulthood. Further, even within youth who receive GAC during adolescence, those who begin earlier in adolescence have lower rates of depression diagnosis, self-harm, and suicidality (Sorbara et al., 2020). The emergent body of literature underscores the benefits of early interventions in providing TNB youth with GAC to reduce the burden of psychosocial suffering that is endemic in these young, marginalized populations (Turban, King, et al., 2022; van der Miesen et al., 2020). Based on empirical findings, several major biomedical and scientific organizations—including but not limited to the American Medical Association, the American Academy of Pediatrics, the American Psychiatric Association, the American Academy of Child & Adolescent Psychiatry, the Endocrine Society, and the Pediatric Endocrine Society—explicitly oppose legislation that bans TNB youth from access to potentially life-saving GAC (Turban et al., 2021).

5. Discussion

In contexts characterized by long timescales, informed discussions, and supportive environments, adolescents possess the capabilities required to engage in adult-like cognitive control and decision-making (Fig. 1). However, in contexts in which decisions are made on a short timescale, they do this with less reliability and greater variability, and their decisions may be more heavily influenced by peers, immediate rewards, and affective processes. The latter kind are most often cited in arguments regarding policy and legislature on GAC, however, given certain

conditions - such as being afforded time to gather information and deliberate, and being supported by knowledgeable professionals and caregivers, TNB adolescents can make important health-related decisions, such as whether to begin, delay, or discontinue GAC. Thus, emphasis should be placed on supporting adolescents and providing the proper conditions to ensure they have the time, information, and resources necessary to make an informed decision, rather than enacting barriers to and allocating decision-making authority for GAC (see Ashley, 2023). As outlined in this paper, TNB youth who experience barriers to receiving GAC are at an alarmingly high risk for adverse mental health outcomes, which can affect the course of neurodevelopment itself, and may pose a greater risk to these individuals than the oft cited, but unsubstantiated harm caused by regret of GAC. The discourse and related legislation to enact barriers restricting access to GAC for TNB adolescents ignores this latter point and misrepresents the neurodevelopmental literature. On the contrary, we can leverage this body of work to consider how best to support TNB adolescents through the process while promoting healthy development, which should be a consideration for policy and legislature concerning GAC in adolescents.

Looking forward, an effective healthcare system for TNB youth seeking GAC should include two key aspects: 1) training healthcare providers to provide well-informed and culturally competent care for TNB youth, and 2) effectively assessing the decision-making capacity of TNB adolescents on an individual basis to determine their understanding of interventions, their short- and long-term benefits and risks, and their ability to make medical decisions for themselves with caregiver consent and support. One important consideration in providing thoughtful and beneficial GAC is ensuring that involved clinicians are well-educated on care for TNB youth (for a review of ethical healthcare considerations for transgender patients, see Sundus et al., 2021). Indeed, health care providers are typically the first people to whom TNB youth disclose their identity

(Haimson & Veinot, 2020), yet research reveals that 1 in 3 transgender adults who have interacted with a medical provider in the previous year experienced mistreatment (James et al., 2016). Having these discriminatory and stressful experiences as a child or adolescent deters TNB individuals from accessing necessary medical care and can negatively affect neurocognitive development. Thus, it is critical that healthcare providers receive extensive training and practice in providing culturally sensitive care for TNB individuals. This includes the use of gender-inclusive language in all communication, ensuring that consent is provided before proceeding with any physical examination or procedures, using affirmed name and pronouns, using gender-neutral decor and messaging in clinic rooms, forgoing unnecessary or invasive lines of questioning or examinations, and other considerations to allow all patients to receive care in a safe, empirically sound, and affirming environment (Ding et al., 2020). Second, physicians and other care providers should be well-versed in the interventions available to TNB individuals and how to communicate and practice medical care in a way that is comfortable for patients and their family. Practitioners should feel comfortable providing TNB youth and their families with up-to-date, evidence-based, easily digestible information about associated biopsychosocial changes, side effects, and long-term outcomes from these interventions. In addition, providers should recognize the difficulty that caregivers of TNB youth often face in accepting their child's gender identity and making healthcare decisions related to their gender (Grossman et al., 2021). Thus, it is imperative that clinicians connect caregivers to resources, such as information sources, support groups, and psychological support, in order to help them provide needed support for their child (Hillier & Torg, 2019; Lawlis et al., 2020). Similarly, clinicians should be prepared to provide TNB youth themselves with resources for psychological support as they navigate the complexities of exploring and affirming one's gender.

Another key component of ethically providing GAC to TNB youth, like all other forms of adolescent medical care, is the thorough assessment of medical decision-making capacity on an individual basis. As discussed, it is well-known that while adolescents often make impulsive decisions in emotional contexts or when time is limited ("hot" contexts), many are fully capable of engaging in adult-level cognitive control and decision-making in a supportive context (i.e., in collaboration with caregivers, "cold" contexts). However, neurocognitive development happens at different rates across individuals, and therefore, creating blanket rules or policies about the age at which youth can make critical decisions for themselves is not supported by adolescent neurodevelopmental research or the most recent Standards of Care (Coleman et al., 2022). Instead, there are a variety of existing, evidence-based tools that providers can use to determine the cognitive and decision-making capacity of TNB youth who present for GAC. Several validated structured and semi-structured interview tools exist to assess medical decision-making capacity, including the MacArthur Competence Assessment Tool (Grisso & Appelbaum, 1998; Hein et al., 2014), the Aid to Capacity Evaluation (Etchells et al., 1999), and the Hopemont Capacity Assessment Interview (Edelstein, 1999). These interview tools, along with a thorough clinical interview, can provide healthcare providers with the necessary information to determine whether an adolescent is cognitively capable of understanding the details of the medical procedures under consideration, and whether they can make related decisions with the support of their caregivers and providers. Notably, one study of medical decision-making capacity in transgender youth seeking GAC using clinical interview and the MacArthur Competence Assessment Tool found that 89-93% of adolescents were capable of consenting to treatment (Vrouenraets et al., 2021). By gathering comprehensive information in the process of exploring GAC, clinicians will be equipped

to determine decision-making capacity on an individual basis, a more ethical and scientifically sound option than the proposed bills banning TNB youth from access to GAC.

5.1 Future Directions

As more children and adolescents seek GAC, it is important to pursue related avenues of neurodevelopmental research that can inform policy decisions and care surrounding GAC. Importantly, while puberty and reproductive hormones are widely recognized to play a major role in brain development, we are only beginning to understand their effects on neurodevelopmental trajectories in humans. Studies investigating the neurodevelopmental effects of puberty blockers, such as GnRH agonists, are also needed to understand the impact of this crucial gender-affirming treatment. At the same time, it should be noted that these medications have been FDA-approved and in use for central precocious puberty for many years, and thus are known to be safe and effective. Despite a paucity of studies characterizing the influence of puberty blockers on brain and psychological development, those that exist have shown positive psychological outcomes (de Vries et al., 2014). Further, though little is known about the effects of puberty blockers on decision-making specifically, some work in adults have shown no changes in cognition following administration of these drugs (Matousek & Sherwin, 2010). It is important to note that even if puberty blockers delay puberty, the ability to make decisions regarding long-term care is available early in puberty and adolescent development, as described previously.

In addition to conducting more studies in general to address gaps in the literature, it would be important to build upon the studies that already exist with studies that include larger samples, as well as longitudinal follow-up, to ensure that findings are robust and reproducible. To assist with this, large-scale consortia datasets, such as the ongoing longitudinal neuroimaging study known as the Adolescent Brain Cognitive Development study, are collecting validated measures

of gender identity development in addition to many neurobiological measures, providing a wealth of future opportunities to better understand the brain's contribution to this important process. However, while it is important to conduct these studies, given the high rates of suicidality and adverse mental health outcomes among TNB youth who do not have access to GAC, the needs of these individuals may outweigh unknown potential risks of these treatments and thus should not be put on hold. Finally, developmental neuroscience researchers need to prioritize expanding samples used in research beyond typical binary characterizations of gender to better understand the unique needs and developmental trajectories of diverse TNB adolescents who plan to undergo, are undergoing, or have undergone various aspects of transitioning. These studies will be critical for continuing to update medical guidance on how to provide these interventions to assure the best possible outcomes for these individuals. Finally, it is of critical importance that there be a translational platform for developmental researchers to interface with professionals working within legal, political, and legislative spaces so that guidelines concerning GAC can be informed by empirical research regarding adolescent cognition and decision-making capacity and the conditions in which adolescents are best supported to make well-informed choices.

Figures

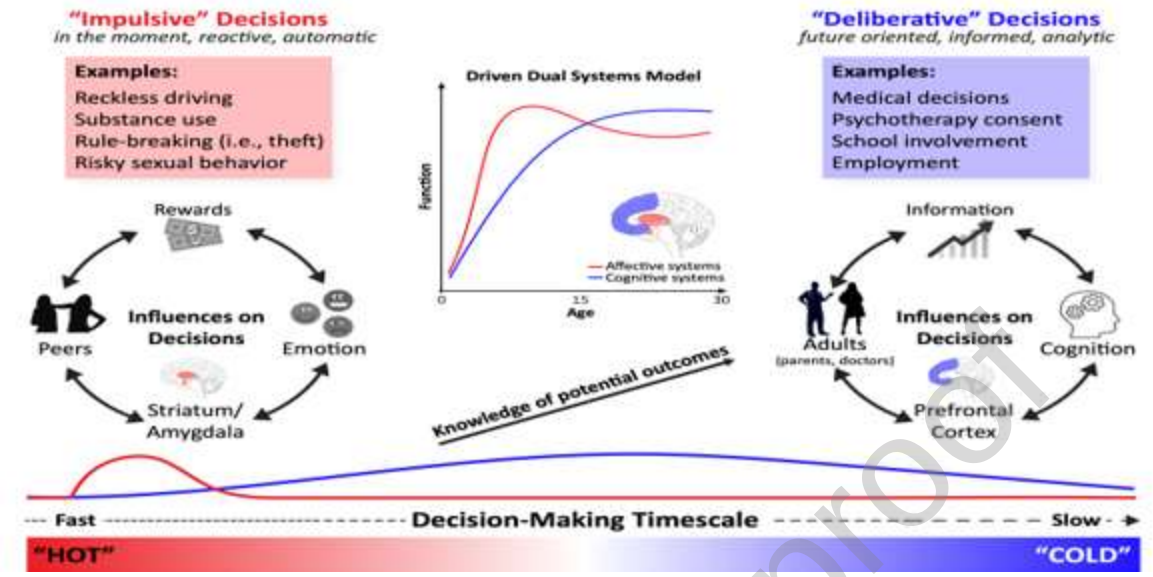

Figure 1. Timescales and Contextual Influences on Adolescent Decision-Making. The left panel (red) illustrates "hot" decision contexts during adolescence, where decisions are made across short timescales, engaging reactive processes, are based on peer, emotion, and reward influences, and engage the striatum. The right panel (blue) illustrates "cold" decision contexts during adolescence, where decisions are made across long timescales, engaging deliberative processes, are based on adult, information, and cognitive influences, and engage prefrontal cortex. The center panel reflects the "Driven Dual Systems Model" of adolescence development, which illustrates that while prefrontal, cognitive systems (blue) are available during adolescence and can be engaged for decisions made in "cold" contexts, they are often driven by affective systems (red) in service of obtaining rewards, primarily in "hot" contexts.

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Data Availability Statement

Due to the nature of this article (narrative review), there is no data to be made available.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper