"Sex versus Gender: A biological location for gender, not sex.

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INTRODUCTION

One thing we can be sure of when it comes to discussing human sex differences and behavior is it “remains an exciting yet challenging task that should occupy researchers for decades to come” (Zell, Krizan, & Teeter, 2015, p. 18). The debates are certainly not yet over (Fine, 2020).

The problems with 'difference' research have been well documented. Confounding results have been attributed to inconsistent definitions, categories vs. dimensions, fixed vs. flexible difference, false positives, small sample size, small effect size, and animal comparisons to humans (Fine, 2020; Hyde, 2005).

Concerning effect size, a significant amount of research supports the 'similarities hypothesis' (Hyde, 2005, 2014), which states that differences in most, but not all, psychological variables are small (Joel, 2011; Hines, 2011). Of critical relevance to this current article is the phrase 'not all.' Concerning animal studies, differences in human and animal brains have shown similar comparative morphology (Guillamon, Junque, & Gómez-Gil, 2016). Animal studies show neural and endocrine systems that likely account for the development and sensitivity of gendered parental behavior *across the lifespan* (Champagne & Curley, 2016; Lonstein et al., 2014). Indeed, gender is a concept relevant solely to humans, however. At the same time, this paper does not deny psycho-social influences on postnatal gender. It locates an uninfluenced prenatal gender as biological and located initially in a physiological place unrelated to later psycho-social influences. With this in mind, and due to ethical restrains in human studies, the reductionist study of animals can be legitimate in searching for understanding in the endocrinology and neurobiology of, for example, nurturant behaviors that are universal across many species and may underpin human behavior (Lonstein et al., 2014).

AIM

This review began with questions. Considering most species consist of two sexes and only females mammals fall pregnant and lactate, it seems logical to ask why would there not be innate cognitive differences relative to the physical differences in the reproductive processes? If so, could we label this difference 'gender,' and could a part or parts of the brain comprise this 'gender'?

The realization that the similarities hypothesis of a sex/gender mosaic (see later) does not account for all human behavior brought focus to this review allowed us to;

(1) split the behavioral domain of the general cognitive mosaic of functions such as reasoning, organization, and execution of complex thoughts, from those cognitions explicitly related to reproduction;

(2) examine the possible location of biological origins for those cognitions associated with reproduction to examine whether they are dimorphic;

(3) present the case that dimorphic neural regions and their associated behaviors are the sources of gender;

(4) examine the same regions in the trans community for dimorphisms. This would support or otherwise the biological source of gender in both the cisgender and trans communities.

Our review will suggest the sense of a gendered self is related to cognitive dimorphic behaviors under the heterogeneous influence of neural networks in the reproductive axis.

Selected definitions / abbreviations

ACC - anterior cingulate.

Cisgender - denoting a person whose sense of identity corresponds with their sex assigned at birth.

Ciswoman – a person whose sense of identity corresponds with their female sex assigned at birth.

Cisman - a person whose sense of identity corresponds with their male sex assigned at birth.

CNS - central nervous system.

CTh - cortical thickness.

DTI - diffusion tensor imaging.

DMN - default mode network.

ER - estrogen receptor.

fMRI - functional magnetic resonance imaging.

MRI – magnetic resonance imaging.

FtM – female to male (female sex assigned at birth).

MEG – magnetoencephalography.

MtF – male to female (male sex assigned at birth).

RA - reproductive axis

GnRH - gonadotropin-releasing hormone.

LH - luteinizing hormone.

FSH - follicle-stimulating hormone.

GM / GMV – gray matter / gray matter volume.

PFC - prefrontal cortex.

WM – white matter.

sMRI – structural magnetic resonance imaging.

mPFC - medial prefrontal cortex.

ER - estrogen receptor.

vMRI – volumeric MRI.

HPG - hypothalamic-pituitary-gonadal axis.

HPA - hypothalamus-pituitary-adrenal axis.

MPOA - medial preoptic area of the hypothalamus.

POA - preoptic area, a region of the hypothalamus.

INAH3 - third interstitial nucleus of the anterior thalamus.

BNST - the bed nucleus of the stria terminalis.

T – testosterone.

Centuries-old categories

Two sexes and two genders have been unproblematic in the everyday fabric for as long as recorded history, at least for those who conform. However, the notion of 'a gendered self' only seems explicable philosophically. Indeed, it is generally agreed our sense of maleness or femaleness resides in the brain (Legato, 2018), and the anatomical location for gender has been considered the brain (Bao & Swaab, 2011). Nonetheless, “the factors that create the gendered brain and gender identity are not yet clearly defined” (Legato, 2018, p. 65).

Terminology

In discussing sex and gender, language matters (Joel & Fausto-Sterling, 2016). The terms 'sex' and 'gender' remain actively entangled with each other, and neuroscience has not provided a reasoned account for where sex ends and gender begins (Kaiser, 2012), while psychology has actively presented them as the blended notion of sex/gender. Avoiding the conflation of the categories of sex and gender (Francis, 2012) inspired some 21st-century thinking, yet from scientific to lay communities, definitions of 'sex' and 'gender' remain confusing and divisive.

Sex

Much like the necessity to attain a patient's sex on admission to a hospital emergency department, this article will keep 'sex' as initially defined by Unger (1979) as that of the body's obvious physical and reproductive anatomy only. The brain, as a sexed organ, is discussed later.

Gender

This article maintains a separation of bodily sex separate from gender. It defines gender as cognitive but does not use it as a term for social expectations or social roles.

We present a framework for gender as the subconscious neurological consequence of the reproductive axis (RA). These networks control both the physical and cognitive behaviors relevant to reproduction.

Dimorphic

The term 'dimorphic,' meaning occurring in two distinct forms, is used in this article for significant differences with some overlap (McCarthy & Konkle, 2005).

Canalized

“Most species maintain abundant genetic variation and experience a range of environmental conditions, yet phenotypic variation is low” (Siegal & Bergman, 2002, p. 10528). In this review, canalized psycho-neuroanatomy refers to that which is moderately focused on male and female endpoints to enhance sex differences.

1. SEX / GENDER AS MOSAIC

This paper focuses on universal early sex differences in behavior unrelated to outside influences and away from the behaviors now widely accepted as a mosaic amongst the sexes.

Questions about sex differences remain; from what, and from where specifically could a gendered self-originate? “How is it the genetic and hormonal components of bodily sex create two distinctly different reproductive systems—and yet human male and female behavior shows itself to be flexible and surprisingly similar?” (Fine, p. 1, 2020) We can as reasonably ask, considering we do not have heteromorphic sex chromosomes and only females endure the marathons of ovulation, pregnancy, and lactation, and males do not, why wouldn't there be differences in innate cognitions relative to the differences in the reproduction burden?

Recent psychological theories have argued there is no natural dichotomy of gendered behavior and propose the notional merging of otherwise distinct categories for sex and gender into a mosaic of sex/gender (Joel & McCarthy, 2017; Rippon et al., 2014). Their arguments favor we desist labelling sex and gender as separate variables and combine them into the singular term - 'sex/gender' (Fine, Joel, & Rippon, 2019; Kaiser, 2012), or 'gender/sex' (van Anders, 2015).

Theoretically, the notion of human behavioral overlap or mosaic removes the need to separate sex and gender. However, the idea that prenatal brains are intersex and belong to a single heterogeneous population is an enormous ambition, according to Pavlova (2017). “While it is well documented that the sexual dimorphism in brain structure and function exists" (Pallayova et al., 2019, p. 271), and is influenced by socio-cultural forces (Eagly & Wood, 2013), is this debate now over, or do we continue to argue the case for gender as biologically distinct from body sex, dimorphic, yet more focussed towards male and female endpoints of a spectrum? These questions raise a conundrum.

A sex/gender mosaic seems to bypass the existence of trans[1] children who identify as gendered opposite to their natal sex as early as age two (Zucker et al., 1997), or age three (Olson & Gülgöz, 2018; Hewitt et al., 2012). It also disregards children who persist post-puberty whose reproductive behavior is not always conventional and late-onset dysphoric individuals with a gender opposite to their bodily sex.

In the absence of a Y chromosome, the embryo's bipotential primordial genital structures develop into female internal and external reproductive organs (Tasopoulos, 2018). This development does not account for post-natal gender incongruence. The dominance of testosterone from around birth results in masculinization of the fetus (Zuloaga, 2009; Wizeman et.al., 2001), yet no matter which is considered the default state for human embryos, male or female (Joel, Garcia-Falgueras, & Swaab, 2020), the brain's high function areas have been labelled initially intersex and not dimorphic (Hyde et al., 2018). Indeed, intelligence levels do not appear sexually dimorphic but rather are mosaic (Halpern & Wai, 2020; Joel & McCarthy, 2017; Jones & Lopez, 2014).

Supporting the similarities hypotheses and in terms of statistical effect size, many differences are small (d=0.20) to moderate (d=0.50) (Hyde, 2005, 2014), with distributions on most variables overlapping by around 84% (Cohen, 1988). Nevertheless;

> Even if other factors such as culture and environment influence gender identity development, evidence from individuals with intersex conditions suggests the critical role of prenatal androgen exposure in sex differentiation of the brain.
>
> (Ristori, 2020, p. 4).

For example, post orchidectomy, brain masculinization may occur in 46,XY individuals with cloacal exstrophy assigned female at birth (Ristori, 2020). Thus, gender identity in the intersex and trans communities as separate from bodily sex makes the notion of a single category of sex/gender awkward, as they do for the totality of cultural and social origins of gender. The presentation of differential cognitive behaviors relevant to reproduction, separate to physical reproductive and high function areas of mosaic behavior, will make the sex/gender notion challenging to maintain.

Professional and non-professional articles continue to present gender as a person's sense-of-self within several intersecting factors and influences (Fiani, 2018; Strauss et al., 2017); however, no one has ventured to suggest what the 'factors' that make gender are, nor from where they might originate.

2. SIGNIFICANT STABLE GENDER DIFFERENCES

Though the 'characteristics' of 'sex-related behavior' relative to the physicality of reproduction are dimorphic, other sex-related behaviors have not been explicitly identified. Some see gender as 'subconscious sex' and an intrinsic part of an individual that hardwires traits of one sex or the other into the brain (Serano, 2016). While there appears to be "…much more overlap in the behavioral phenotypes of males and females especially outside the context of reproduction" (McCarthy, De Vries, & Forger, 2017, p. 24), apart from physical behaviors related to mating, clarification of these 'behaviors' and 'traits' is missing in the literature.

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[1] This community considers any other term other than 'trans' as discriminatory.

Sex-related behaviors

Although still contested, small to moderate gender differences are well established in more than a few areas. At least ten sex differences are reported as moderate to large (d=0.50-0.80), including mental rotation ability, interest in people vs. things, response to noxious stimulation, visually induced fear, peer attachment, confidence in physicality, and aggression (Zell, Krizan, & Teeter, 2015). Pain tolerance seems to be differential, at least anecdotally, though "genetic effects have been unable to fully explain the variation in pain sensitivity" (Castillo-Fernandez et al., 2014, p. 12). Furthermore considering differences are also likely context-dependent across domains (Del Giudice et al., 2012), small gender differences should not be regarded as trivial (Zell, Krizan, & Teeter, 2015). Additionally;

> Even behaviors such as depressive symptoms with statistically modest effect sizes (e.g., d . .36) can result in a multifold risk of suffering from clinically profound distress in one sex, e.g., in females.
>
> (Vigil, 2009, p. 381).

Neurotological imaging reveals how the human brain is organized into interconnected compartments or regions. The human Brainnetome Atlas has subdivided the entire human brain into 210 cortical and 36 subcortical subregions (Fan et al., 2016). Some regions are dimorphic between the sexes.

> While acknowledging there are reliable sex-related differences in the organization of the neurological substrates underlying [for example] decision making and emotion, it has been challenging to speculate on biological, evolutionary, or psychosocial reasons driving these differences.
>
> (Reber & Tranel, 2017, p. 275).

These authors offered that different parental biological and social roles in childbirth and childrearing may play a role (Reber & Tranel, 2017).

By acknowledging the bio-psycho-social model of identity development, the origins of sex differences in the brain (both structural and functional) are more attributed to the combined effects of hormones, genes, epigenetics, and the social environment (Ratnu et al., 2017; Eagly & Wood, 2013). This line of thought is now favored in research into gender identity (Auger, & McCarthy, 2017; McCarthy, Pickett, Van Ryzin, & Knight, 2015). Nonetheless, biology and culture work hand in hand, and it appears difficult to impossible to separate the influences of one from the other (Joel, Garcia-Falgueras, & Swaab, 2020; Fine, Joel & Rippon, 2019). Further, "gender incongruence is a complex multifactorial trait, involving intricate interactions among steroids, steroids receptors, and multiple genes and polymorphisms" (Fernandez et al., 2020, p. 498).

On the other hand, what do universal, stable, significant gender differences mean? This article has not abandoned dimorphic behavior differences and presents sex, gender, and behavior most relevant to reproduction, as significantly female-typical or male-typical (O'Hanlan, Gordon, & Sullivan, 2018; Sisk, 2016; Mustanski et al., 2005). This dimorphism should not be unsurprising in a sexually reproducing mammalian species.

Universal early sex differences in cognitive behavior, unrelated to outside influences and removed from the behaviors accepted as a mosaic, could arguably be those relevant to reproduction and survival. Following research into the differences in neural and endocrine development, differences in the reproductive burden on ciswomen compared to cismen, and research into the trans community, this article presents a case for the physical location of an internal and perceptual sense or feeling of gender associated with the RA and the cognitive behaviors differentially linked with reproduction throughout the lifespan.

From the first post-natal days, sex differences are expressed in human behavior. Female neonates and young girls prefer looking at human faces, while male infants look more at mechanical mobiles (LoBue & DeLoache, 2009; Connellan et al., 2000).

> Day old neonates demonstrate sexual dimorphism in both social and mechanical perception. Male infants show a stronger interest in mechanical objects, while female infants show a stronger interest in the face. The male preference could not simply be for a moving stimulus, as both stimuli moved.
>
> (Connellan et al., 2000, p. 116).

Toy preference, faces versus things, and play preferences in children are apparent as early as age six months (Kung et al. 2018; Berenbaum & Beltz, 2016; Jones & Lopez, 2014; Alexander, 2003) and all with scant social experience. It is also possible "that boys like toys that can be moved in space" (Hines, 2011, p. 74). Studies with monkeys baring similar results, highlight how toy preferences cannot be explained by simply by social pressure (Bao & Swaab, 2011). Overall, it seems that gender identity, sexual orientation, other behaviors, and brain disorders are programmed prenatally as dimorphic in the brain (Bao & Swaab, 2011).

To associate gender with the RA, the RA must be dimorphic and canalized towards female and male endpoints of a spectrum, as are, for example, sexual orientation (Savin-Williams, 2014) and intersex conditions (García-Acero et al., 2020). If specific brain regions are essential to specific cognitions, and these regions are dimorphic, it follows that the associated behaviors are likely dimorphic. This process, termed 'equifinality' by its creator, is defined as a common outcome derived from different pathways. So although gender is a complex multifactorial trait where outcomes may not be linearly determined, as we shall see, a common outcome can derive from different pathways. For example, the development of a normal organism from a whole, divided, or two fused ova (Von Bertalanffy, 1993).

Reproductive Axis

The reproduction axis stems from the testes, ovaries, and on to the limbic system. Traditionally the RA consists of five main components: the extra-hypothalamic central nervous system (CNS), pituitary, testis, ovaries (Acevedo-Rodriguez et al., 2018; Pejić et al., 2015; Klein et al., 1994), which are all target organs of sex steroid hormones (Ruiz-Cortes, 2012; Wierman, 2007). Under a broad umbrella, the RA can be considered as consisting of any organ in the interconnected network of neurons targeted by sex steroids.

The RA is a tightly regulated feedback loop paramount to reproductive potential (Acevedo-Rodriguez et al., 2018; Couse et al., 2003; Klein et al., 1994). Control of the RA occurs at all levels. It is particularly important for female reproduction, where neuroendocrine control lays with gonadotropin-releasing hormone (GnRH) neurons dispersed from the hypothalamic region of the limbic system (Alzahrani et al., 2019; Acevedo-Rodriguez et al., 2018). Increases in GnRH are required for a luteinizing hormone (LH) surge and consequently, ovulation (Acevedo-Rodriguez et al., 2018). The RA further coordinates the production and secretion of the gonadotropins, including luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the anterior pituitary which in turn stimulates the release of the sex steroids, androgens, estrogens, and progesterone produced primarily by the ovary, corpus luteum, and adrenals (Blair et al., 2015).

Regulation of reproductive circuitry in the brain includes kisspeptin neurons. Acevedo-Rodriguez et al. (2018) report kisspeptin detection primarily in two regions of the hypothalamus and preoptic area. It is an important hormone that starts the release of several other hormones. Kiss1 gene expression is more generous in females than males who do not show a LH surge (Acevedo-Rodriguez et al., 2018).

Estrogen and androgen receptors show high distribution levels in the pituitary, hypothalamus, amygdala, ovaries, testes, and uterus (Denley et al. 2018; Swaab, 2004; Sato et al., 2004; McEwen, 2001); in other words, in the reproductive axis overall.

The hippocampus, hypothalamus, amygdala, and other areas are repeatedly shown to be dimorphic in post-mortem and in-vivo imaging studies (Lotze et al., 2019; Goldstein et al., 2001). To investigate whether there are distinct neuroanatomical signatures of cisgender and trans male and cisgender and trans female gender identity, a sMRI study of gray matter (GM) tissue maps demonstrated “the neuroanatomical sex classifier trained on the cisgender participants (FC vs. MC) correctly separated biological women from men” Baldinger-Melich et al., 2019, p. 1348). Unlike other similar studies, the authors could not detect a distinct neuroanatomy for gender incongruence (Baldinger-Melich et al., 2019).

This current paper considers the cortex and all its subsystems in the limbic region - hippocampus, amygdala, and hypothalamus - as parts of the RA. Continuing with a review of the literature will demonstrate how the RA is dimorphic or canalized towards female and male endpoints.

With its inter-connectivity with subcortical structures and its commanding function with all types of behaviors (Guillamon, Junque, & Gómez-Gil, 2016), the cortex makes it one prime location to understanding gender identity.

Cortex

Asymmetries for microstructure and functional connectivity between the sexes are a well-documented phenotypic variable in humans' brains (Grabowska, 2017). For example, a study of individuals between 7 and 87 years of age revealed, independent of brain and body size, greater cortical thickness in females in specific temporal regions (Sowell et al., 2007). Cortical thickness (CTh) and diffusion tensor imaging (DTI) show that the thickness presents an F>M (Guillamon, Junque, & Gómez-Gil, 2016).

Prefrontal Cortex

The frontal lobes are enormous, 25–33% of the entire cortex (Stuss, 2011). The prefrontal cortex (PFC), with its subcortical connections in the limbic system, is a neurological structure heavily involved in the social brain's decision making, emotion regulation, social functioning, sexual orientation, and behaviors relevant to reproduction. For example, sex significantly modulates functional lateralization of emotion and decision making in regions such as the ventromedial prefrontal cortex (vmPFC) and amygdala. This finding follows functional lateralization patterns of well-studied cognitive phenomena. In verbal fluency women tend to outperform men and in spatial processing, men outperform women (Reber & Tranel, 2017).

Men tend toward higher physical abilities for spatial cues and navigation. A meta-analytic study to quantitatively synthesize quantitate empirical research on the magnitude of gender differences in 3-D mental rotation ability, estimates the overall average effect size for gender difference of a male is about 0.57 (moderate d=0.50) standard deviation higher than a female. However, much like gender studies generally, the authors found difficulty in synthesizing mental rotation ability in the literature as it may vary due to the measure used. Inconsistent reporting practices limited the number of studies to 40 (Maeda & Yoon, 2013).

Differential anatomical connectivity in emotion processing make vital contributions to generating responses to negative emotions, explicitly concerning limbic regions (Hahn et al., 2015). Anger, anxiety related to emotional conflict activates the anterior cingulate (ACC) and the - medial prefrontal cortex (mPFC) (Etkin et al., 2011). General emotional disturbances may be obvious in disruption of subcircuits of the amygdala and pregenual ACC (Marusak et al., 2016).

In discussing neuroimaging of the prefrontal cortex for responses associated with the social brain, such as emotion perception or body-language reading, females were quicker in their recognition (Pavlova, 2017). There is an indication of sex differences in projections from the prefrontal cortex to the thalamus; the cortex's relay center (Xin et al., 2019).

In an in-vivo MRI study of 2,838 subjects age range 21–90 years, self-identified as 'sex' as 'man' or 'women', with exclusion criteria for stroke, multiple sclerosis, epilepsy, Parkinson's, dementia, cerebral tumor, intracranial cyst or hydrocephalus, the findings for magnitude, location, and direction of sex differences of gray matter volume (GMV) provide a stimulus in the measurement of sex-specific differences in cognitive, emotional, and behavioral differences between men and women (Lotze et al., 2019).

The default mode network (DMN) of the brain are regions in the posterior and anterior cortical structures and whose activity is high when the mind is not engaged in external tasks. Features of functional connectivity within the DMN contribute most to gender prediction (Zhang et al., 2018). Though the authors caution it is difficult to predict gender identify directly via imaging studies because they found the significant sex differences effecting functional connectivity (FC) were on a spectrum, and there were other networks also showing high contributions (Zhang et al., 2018).

Following the different morphologies present in multiple regions of the interconnected CNS in cisgender studies, it would be unreasonable to argue any distinct region of the CNS, such as the cortex, serves as the entire neurobiological location for gender. For example, the bed nucleus of the stria terminalis (BNST) located in the basal forebrain, is connected to the amygdala and hippocampus and the hypothalamic and brainstem nuclei. It also has reciprocal connections with the and prefrontal cortex (Crestani et al., 2013).

Further, for example, the hypothalamic-pituitary-gonadal (HPG) axis (discussed later) does not sit inside the limbic system disconnected from the rest of neuroanatomy. Receptors for the HPG axis hormones that regulate fertility are expressed throughout the brain and, in particular, the limbic system (Meethal & Atwood, 2005).

Frontal-subcortical circuits constitute a closed-loop of anatomically segregated neurons, while their functional connectivity incorporates open-loop elements (Bonelli & Cummings, 2007). Regions of the CNS that relate to the development of body perception are incorporated in the frontoparietal cortex, amygdala, hypothalamus (Uribe et al., 2020; Manzouri, Kosidou, & Savic, 2017; Savic & Arver, 2011; Northoff et al., 2006).

Circuits mediating limbic functions, such as the projections from non-circuit cortical areas, thalamic nuclei, and the amygdala nuclei, have connections to other limbic areas, whereas structures and circuits involved in executive function and cognition interact (Bonelli & Cummings, 2007).

The limbic system

The limbic system (the emotional, nervous system), first described in 1964, is one of the most studied functional networks in the social brain (Yang, Comninos, & Dhillo, 2018). The cortical and subcortical limbic system is a ring of tissue on each cerebral hemisphere incorporating the amygdala, orbitofrontal gyrus, cortical regions, hypothalamus, cingulate gyrus, and hippocampus. The main components are the hippocampus, the amygdala, and the hypothalamus (Roxo et al. 2011).

The limbic system is structurally dimorphic (Zaidi, 2010; Kruijver et al. 2000) and often studied in the relationships between brain and mind (Wu & Shah, 2011). The process of dimorphic neonatal sexual differentiation shapes brain regions involved in regulating behavior relevant to reproduction in the limbic system nuclei (Sakata & Crews, 2004). The limbic system zones develop differentially (Zaidi, 2010; Sakata & Crews, 2004) and are stable across the lifespan (Simerly, 2010, 2002;

McCarthy & Konkle, 2005).

In the Lotze et al. (2019) study previously mentioned, more GMV in women was

> "prominent in medial and lateral prefrontal areas, the superior temporal sulcus, the posterior insula, and orbitofrontal cortex. In contrast, more GMV in men than in women was detected in subcortical temporal structures, such as the amygdala, hippocampus, temporal pole, fusiform gyrus, primary visual cortex, and motor areas (premotor cortex, putamen, anterior cerebellum)."
>
> In men (men > women), on average larger GMV was evident in bilateral temporal areas, such as the parahippocampal gyrus, the hippocampus, the amygdala, the temporal pole, and the fusiform gyrus, as well as the bilateral putamen, anterior cerebellar, and left primary visual cortex."
>
> (Lotze et al., 2019. p. 1-2).

Effect sizes for men > women ranged from small (0.27) to moderate (0.49) (Lotze et al., 2019).

Though the authors did not measure cognitive or behavioral data, they highlight that "increased GMV is associated with better functioning in the cognitive domain" and that prefrontal areas (GMV F>M) "are functionally important for executive functioning, such as planning, working memory, inhibition, mental flexibility…emotional control, moral considerations, and processing of language" (Lotze et al., 2019, p. 5).

Amygdala

This RA region is broader in cismen and with a higher density of androgen than estrogen receptors (see, for example, Halpern, 2013). A growing number of studies show the amygdala as crucially involved with enhanced memory of emotionally arousing events. An fMRI study of arousal rating from neutral to negative imagery, the left hemisphere amygdala, but not the right, demonstrated better memory performance and increasing arousal ratings in women than in men following imagery of function concerning memory for emotional events (Cahill et al., 2004).

Though a recent meta-analysis of the literature for studies reporting the amygdala volume concluded, the amygdala was not sexually dimorphic (Marwha et al., 2017), the functional images in the Cahill et al. (2004) study were spatially normalized.

Hippocampus

The hippocampus has often been reported as dimorphic. As a region of the RA, portions of the hippocampus are more extensive in women, with a higher density of estrogen than androgen receptors (Ristori, 2020). However, a recent sMRI study concluded that structurally it is not dimorphic (Tan et al., 2015). Nonetheless, sex steroids are highly dimorphic for functional outcomes. Estrogen receptor (ER) expression occurs across various cell types of the hypothalamic-pituitary circuit, and emerging evidence indicates that steroid hormones impact the cortex, hippocampus, and amygdala (Acevedo-Rodriguez et al., 2018).

The hippocampus is a brain area critical for learning spatial cues. Animal studies point to discrete sex differences "within a hippocampal field critical for memory formation, that are likely to be centrally involved in the encoding spatial information." (Wang et al., 2018, p. 7945). Findings suggest exogenous estrogen mobilizes ER signalling in excitatory pathways in both sexes, but there is dimorphism in estrogen receptor (ER) trafficking that triggering "significant contributions from ER in females only" (Wang et al., 2018, p. 7947).

Pituitary

While not structurally a region of the limbic system, the pituitary has a pivotal role in the HPG axis. The pituitary is a master gland regulating hormone levels in the body. The pituitary gland hormones send signals to the thyroid gland, adrenal gland, ovaries, and testicles to stimulate or inhibit their hormone production (Hou, 2019; Kopsida et al. 2009).

The pituitary is a stress-related region of the brain (Macmaster et al., 2007). In-vivo imaging of volumetric studies has recorded evidence for gender differences in pituitary anatomy. A balanced (n=77 males and 77 females) age-matched (seven to 35-year-olds) vMRI study of healthy subjects found pituitary gland volume correlated strongly with age.

Pituitary gland volume differed between sex/age groups with F>M in the 14-17-year-olds. Male pituitary gland volumes were smaller in the 7 to 9 year old and 10 to 13 year old compared to the 22 to 35-year-old males. Within the youngest group of females (7 to 9 years of age), smaller volumes were observed than all other female age groups. “Additionally, the 10 to 13-year-old females were smaller than 14 to 17-year-olds and 22 to 35-year-olds” (Macmaster et al, 2007, p. 5). The authors suggested the root of the sex difference in pituitary volume may lie in the earlier onset of puberty in girls compared to boys.

Despite the lack of analysis of pituitary volume corrected for body size, the study concluded that because tissue resolution was very similar across sequences, the pituitary gland's sex and age effects were significant (Macmaster et al., 2007). Consistent with this research, non-linear associations between age and pituitary gland volume differ by sex (Whittle et al., 2020).

Hypothalamic-pituitary-gonadal (HPG) axis

A subsystem of the reproductive axis relevant to reproduction and within the limbic system is the hypothalamic-pituitary-gonadal (reproductive gonadal) (HPG) axis (Acevedo-Rodriguez et al. 2018).

The HPG axis orchestrates physiological processes required for reproduction (Yang, Comninos, & Dhillo, 2018). The HPG axis's nature was first proposed in the early 1930s (Meethal & Atwood, 2005). Reproduction governed by the HPG axis is distinguished here from the hypothalamus-pituitary-adrenal (HPA) axis. The HPA axis is a looped neural network between the hypothalamus, pituitary gland, and adrenal glands that plays a regulatory role in the menstrual cycle (Roca et al., 2003) and managing the body's response to stress (Rose, 2010). Stress activates the HPA axis, which in turn can suppress the reproductive system at multiple levels and, in particular, the HPG axis (Calisi et al. 2018). Anecdotally, this is the reason why many women athletes face temporary amenorrhoea.

Gonads function differently because of differences in the HPG axis, and there are functional differences in various activity centers in the brain relative to the HPG (Acevedo-Rodriguez et al. 2018). Activation of the hypothalamic-pituitary-gonadal (HPG) axis resulting in gonadal maturation signifies the onset of puberty (MacMaster et al., 2007). This activation leads to increases in levels of luteinizing hormone, estradiol (females only), follicle-stimulating hormone (females only), and testosterone (Peper et al., 2010). Although the HPG axis is possibly linked to and modulated by stress hormone signalling from the HPA axis (Luine, 2014), and there are gender differences in response to stress (Hinojosa-Laborde et al., 1999); this discussion is restricted to the HPG axis as it is a well-regulated endocrine system allowing for successful reproduction (Acevedo-Rodriguez et al. 2018).

Structural sex differences in the human CNS may be influenced by differential hormone exposure. These differences may involve the corpus callosum, anterior commissure, third interstitial nucleus of the anterior thalamus (INAH3), and BNST (Zuloaga, 2009). Both the BSTc and INAH3 are reportedly larger in men than in women (Smith et al., 2015). The presence of HPG hormones, cognate hormones, and their differential receptors strongly suggests their related signalling elicits dimorphic structural and functional instructions during neural development and adult reproductive life (Meethal & Atwood, 2005; Simerly, 2002).

The HPG axis resets at birth due to the significant decline in estrogen levels following the fetus's disconnection from the placenta (Rogol, 2020). However, disruption of the RA prenatally, specifically the HPG, and during mini-puberty (the 3-6 post-natal months) can lead to anabolic changes in linear growth, genital growth, and tissue growth in sexually dimorphic body composition (Rogol, 2020; Kurtoğlu & Baştuğ, 2014). This disruption implies the RA's significant role in the overall development and that disruption of the RA could also lead to gender incongruence.

Connectivity / Connectome

Recent advances in imaging have allowed for the use of resting-state fMRI to explore the functional connections of brain networks, or the communication architecture of the spatially distributed, but functionally linked brain regions (Van Den Heuvel & Pol, 2010).

The perception of one's body and one's self (Samuels, 1986) "heavily involves cerebral midline structures incorporating a parieto-occipital 'body detection"'network" (Manzouri, Kosidou, & Savic, 2017, p. 1005). Studies suggest own body recognition or perception as connectivity phenotypes (Uribe et al., 2020) may be mediated by the communication architecture or interacting brain networks (Feusner et al., 2017). The frontoparietal region related to the own body perception shows sex differences (Uribe et al., 2020; Ritchie et al. 2018).

One contemporary DTI connectivity study concluded that during development, within-hemisphere (intra-hemispheric) connectivity typifies male brains with networks that are transitive, modular, and discrete, whereas inter-hemispheric connectivity and greater cross-hemispheric participation typifies female brains. The study included DTI of 948 subjects aged 8-22 (mean age males 14.9, females 15.1 years). The authors claim overwhelming support for the hypothesis that male brains are heightened for intrahemispheric communicating, and female brains for interhemispheric communication (Ingalhalikar et al., 2014). These results were supported further in another large cohort of 2750 females aged 44 –77 years and 2466 males aged 44 – 77. Female > male connectivity within sensorimotor and visual cortices and "some evidence for male>female connectivity in sensorimotor and visual cortices" (Ritchie et al. 2018, p. 2970). Although participants' age was anywhere from 'young' to 70+, the evidence is in line with findings that some sensory and cognitive aspects are known to differ between the sexes and with male brains more asymmetrical, and female brains more bilaterally organized (Grabowska, 2017).

Tunc et al. (2016) conceded that reliance on social and cultural effects seem insufficient in explaining sex-induced variance in behavior. Diffusion-weighted magnetic resonance imaging (dMRI) study of the structural connectome subnetworks in 900 participants (491 females mean 15.2 years of age, and 409 males average 14.9 years) revealed higher inter-hemispheric connections in females, and higher intra-hemispheric connections in males. The resulting conclusion for males was increased structural connectivity "related to the motor, sensory and executive function subnetworks in males. In females, subnetworks associated with social motivation, attention and memory tasks had higher connectivity" (Tunc et al, 2016, p. 1). Further, "males were accurate on spatial and language tasks, while females were faster on non-verbal reasoning" (Tunc et al, 2016, p. 4). "In moto and sensorimotor tasks, males performed faster. Although females were faster in emotion identification, unlike previously reported results, the difference was not statistically significant' (Tunc et al, 2016, p. 4). "Hence, it is clear that the behavioral differences between males and females are accompanied by related structural differences across their development" (Tunc et al, 2016, p. 6).

The dimorphic differences in the RA discussed above are significant because of their association with cognitive behaviors related to reproductive behavior.

Biological / evolutionary purpose of differences

One argument proposes sex differences might be considered adaptations that serve particular evolutionarily and social needs. This current proposal supports the hypothesis that innate based difference enables competencies that match gendered roles, particularly emotional/empathic skills in females and mathematical/spatial skills in males. That is, dimorphism forms the somatic and neural foundations for sex-differentiated skills or preferences (Grabowska, 2017).

A recent literature review of results from 142 metanalyses on brain, sex, and or gender identified 22 studies reporting data on dimorphic brain structure and function. According to the authors of this decisive study, there is an increasing body of research suggesting sex differences in several areas of human brain performance exist, i.e., several capacities for performance or behavior and their associated cerebral regions are dimorphic (Pallayova et al., 2019).

Based on their review, Pallayova et al. (2019) suggest that differences in the amygdala can explain female superiority in long-term memory retrieval (as opposed to visual-spatial memory). Their data suggest:

a. Males and females recruited different prefrontal regions during emotional tasks: males the bilateral prefrontal and females the bilateral amygdalae. This suggests valuating emotional stimulus plays a vital role in males' strategy in emotional response, whereas, a females' strategy is mainly affected by an emotional stimulus perception.

b. Dimorphic lateralization of brain function suggests the left hemisphere in females processes nonverbal tasks more frequently than in males.

c. Males significantly activated the left superior frontal gyrus during visual-spatial cognition tasks. Females activated the left superior parietal lobule. This reveals further dimorphism in lateralization.

d. For females, processing of spatial information revealed better recovery of objects by location in the right than the left visual hemispace, possibly related to their lower visual-spatial functioning.

Basic cognitive control is sex-specific (Pallayova et al., 2019). Reviewing association studies of Y chromosome subjects who share alleles from parents sharing common ancestral clans, the authors argued the Y chromosome might exert a considerable influence on brain function due to inheritance playing out in sex-biased neuropsychiatric disorders (Kopsida et al., 2009).

Anxiety as a cognitive function relative of emotional processing. It reflects processes involved in the negative adaptive regulation of behavior, and cognitive control and is significantly greater in women with than in men. The HPG axis orchestrates physiological processes required for reproduction, and the sex difference in the negative anxiety reflects the influences of gonadal hormones, particularly ovarian hormones (Yang, Comninos, & Dhillo, 2018) as well as in fear conditioning (Glover et al., 2012). Neural regions involved as a source of negative anxiety include the anterior cingulate cortex, midcingulate cortex, prefrontal cortex, and supplementary motor areas (Moser et al., 2016).

Reproductive Behavior

The past decades have seen the pendulum of sex differences swing through alternative affirmation and denial (Kret & De Gelder, 2012). Of the many sex differences found in the central nervous system, around 10 can be linked to sex differences in behaviour (Zell, Krizan, & Teeter, 2015). Of most all other sex differences, it is unknown precisely "what advantage the dimorphism gives males and females in terms of function" (McCaethy et al., 2017, p. 24). Interestingly, however, and perhaps hinting at an answer, several cognitive behaviors relevant to reproduction are differentially associated with the limbic system (Hoffman, 2013; Bonelli & Cummings, 2007) as part of an integrated network of intrinsic links that unite sex, emotion, to facilitate species survival (Yao et al., 2017). Recent consistent findings with different samples point to the most significant and most stable gender differences occurring in several areas. Some examples include emotion processing and motivation (Tunc et al., 2016), face recognition, aggression, sexual arousal, anxiety, and fear conditioning (Marwha et al., 2017; Heberlein et al., 2008; Swain et al., 2007).

Both men and women can show the biological 'fight-or-flight' pattern of arousal. With a focus on evolutionary selection pressures benefiting both self and offspring, there are sex differences in the consequent behavior with women showing more 'tend-and-befriend' (Verma et al., 2011).

Fight (aggression) typically characterizes men's behavior under stress, and women's by tend or flight (social withdrawal, substance abuse). This difference may demonstrate how emotional expression for males and females may recruit different cerebral networks (Kret & De Gelder, 2012).

The ongoing sexual division of labor highlights that males and females may employ their innate abilities to procure resources and achieve cooperation in the care of offspring while also under socialization and culture (Tay et al., 2019). The well-established small to moderate gender differences in more than a few areas are easily relatable to dimorphic reproductive cognitions instead of the general cognitive mosaic. For example, many studies support sex differences in aggression (Hyde et al., 2018; Zell, Krizan, & Teeter, 2015; Card et al., 2008; Cohen-Bendahan et al., 2005), and empathy (Hines, 2017; Chaplin, 2015; Kret & De Gelder, 2012; Kopsida et al., 2009; Swain et al., 2007; Chapman et al., 2006).

The review by Pallayova et al. (2019) highlights significant sex differences in gray matter to white matter ratios, the amygdala, hypothalamus, hippocampus, frontal cortex, and there differentiated functional interconnectivity. In answering what particular evolutionarily / socially purpose these differentials concur, it is not a long bow to draw in suggesting the behavioral arenas of sensorimotor, emotional perception and processing, mathematical and visuospatial abilities, traditionally relate to reproduction. We will explore the two behavioral areas of aggression and empathy to demonstrate behavior especially relevant to reproduction.

3. SEX-SPECIFIC BEHAVIOR

Earlier studies have reported no differences in the human connectome that could locate gender. The connectome incorporates the cerebral network's overall communication architecture, a description of brain connectivity and function rather than anatomical or structural difference.

The dimorphic RA incorporates the brain areas processing cognitions related to reproduction, i.e., within the two dimorphic reproductive systems. In other words, these cognitions are gendered and may be reinforced or not by outside factors such as culture and social learning.

The surfeit of findings replicated with different samples points to the sex of an individual significantly modulating cognitions related to reproduction, and how several cognitive behaviors associated with the cortex, limbic system, and reproduction, are focussed towards male and female endpoints of a spectrum we would call 'gender.'

Parenting

Parent and infant gender may vary parent-infant emotional expression. Greater than trivial behavior differences have been presented in the arenas of aggression and sexuality (Hyde et al., 2018), courtship, and care of offspring (Meyer-Bahlburg, 2019). The moderate to large gender differences are notable exceptions to the similarities hypothesis on sex differences with specific bearing.

Hormones are not strictly necessary to express maternal behavior in non-human and human primates. Human females and males of all ages and reproductive conditions can express infant-caregiving behavior (Saltzman & Maestripieri, 2011). Further, it is thought cognitions are the source of the emotional states and individual traits during pre- and postpartum mothering (Lonstein et al., 2014). Nonetheless, the levels estrogen, progesterone, prolactin, oxytocin, and testosterone (T) present in a parent influence variation in parental behavior both within and between individuals (Saltzman & Maestripieri, 2011). The different mix of hormones between males and females throughout the lifespan thus becomes relevant to parenting behavior. As Vigil (2009) suggests, "Perhaps the gender-dependent correlates of neural activity reflect neural predispositions in mothers for responses to preverbal infant vocalizations" (p. 402).

Is there a Female Brain?

Only human females acquire pre- and postpartum neurology. Female hormones are associated with maternal behavior in animals, non-human and human primates (Champagne & Curley, 2016; Lonstein et al., 2014; Saltzman & Maestripieri, 2011; Smith et al., 2012). In particular, estrogen receptors emerge within areas of the limbic system's medial preoptic area of the hypothalamus (MPOA) "in mid to late gestation and reach adult-like levels at the time of birth" (Champagne & Curley, 2016, p. 11). The anterior preoptic area (POA) is the region responsible for cycling GnRH release. At the time of birth, the medial preoptic region (SDN-POA) is sexually dimorphic. Testosterone exposure at around the time of birth causes the volume of the SDN-POA in males to become "several times greater than in females" (Zuloaga et al., 2009, p. 348).

This cyclical release of GnRH from the anterior POA is responsible for pituitary synthesis and release of the gonadotropins, LH, and FSH; both of which "act at a distant target, the gonads, as essential in linking the hypothalamic-pituitary-gonadal (HPG) axis" (McCarthy, De Vries, & Forger, 2017, p. 6).

Estrogen sensitivity within the MPOA defines mammalian maternal behavior across the lifespan (Champagne & Curley, 2016) as well as multiple neural and endocrine systems, in particular, sensitivity to estrogen within the medial preoptic area of the hypothalamus (mPOA) (Champagne & Curley, 2016; Lonstein, et al., 2014). Advanced fMRI studies reveal activation in the postpartum brain areas such as the anterior cingulate and ventral prefrontal cortices, amygdala, hypothalamus, hippocampus, and septum–preoptic area. They also show "how the postpartum human brain responds to infant-related auditory or visual cues" (Lonstein et al., 2014, p. 2414).

Neural and endocrine systems likely account for maternal behavior (Champagne & Curley, 2016). Interestingly, the human cochlea is sex-typed from an early postnatal age (Braga et al., 2019). Hearing is a sexually dimorphic trait (Shuster et al., 2019; O'Hanlan, Gordon, & Sullivan, 2018). Response to one's infant cry and breastfeeding is associated with greater fMRI activity in some cerebral regions (superior frontal cortex, thalamus, hypothalamus, and amygdala) (Lonstein et al., 2014). Newborn and adult females have greater hearing sensitivity and greater susceptibility to noise exposure at high frequencies (Burke et al., 2020; McFadden, 1998). Lactating mothers perceive noise differently (Lonstein et al., 2014). Could hearing differences also relate to the needs of dependent offspring and infant cues and another dimorphic trait associated with our sense of gender?

Only female humans breastfeed. As we would expect, though, with variety being the norm in human development (Fausto-Sterling, 2018), "not all human mothers are healthy and motivated, and women are heterogeneous in their emotional and cognitive appraisals of infants" (Lonstein et al., 2014, p. 2415). Nonetheless, that does not subtract from the observation that differences responsible for behaviors relevant to reproduction are lifelong and set in utero.

The emotional behaviors most associated with mothering in females are cues of trustworthiness (Whittle et al., 2011) and empathy (Swain et al., 2007), while the remainder are a mosaic (Joel & McCarthy, 2017; Jones & Lopez, 2014). As discussed, women tend toward better social and linguistic skills (Reber & Tranel, 2017; Pavlova, 2017; Chaplin, 2015), while men tend toward higher physical abilities combined with technical, spatial, and navigating (Pallayova et al., 2019; Tunc et al., 2016; Zell, Krizan, & Teeter, 2015; Maeda & Yoon, 2013) which are also arguably relevant to reproduction.

Specific essentially driven behavioral differences in the brain have been presented as limited to factors surrounding reproduction (Joel & McCarthy, 2017; Arnold et al., 2004).

As we noted, overlap in the general behavioral phenotypes of males and females appears widespread (McCarthy, De Vries, & Forger, 2017), however, outside the context of reproduction and apart from *physical* behaviors related to reproduction, clarification of specific 'behaviors' and 'traits' is unclear.

One offer is that "sex differences are sex-specific neuroanatomical underpinnings of some parental behaviors" established neonatally (Joel & McCarthy, 2017, p. 380). Though the authors did not clarify what behaviors are included in 'some,' they added, "the behavior is not expressed before the appropriate activational hormonal milieu is established following mating/pregnancy" (Joel & McCarthy, 2017, p. 380). Others claim this is unnatural, and maternal tendencies are lifelong (Champagne & Curley, 2016) and "most adult mammals are unlikely to approach parturition with no previous parenting experience…they would have received this experience during juvenile alloparenting" and or already be multigravid parents (Lonstein et al., 2014, p. 2419).

Our theory that specific parental cognitions are biologically relevant to reproduction follows the differential development of the limbic system (Zaidi, 2010; Sakata & Crews, 2004; Kruijver et al., 2000). Furthermore, as males of all ages have substantially higher T levels than females (Smith et al., 2015; Zuloaga, 2009), this would include lifespan paternal tendencies.

Can we derive these 'certain' gendered cognitive differences from the surfeit of studies presented related to the differences in the reproduction burden? We may find clues within the knowledge that human neonates are dependent on others for their survival for a very long time.

Physical behavior

Under the broader neo analytic understanding gained from the feminist theory of Nancy Chodorow, we may view sexuality concerning reproduction as a universal and enduring element of the sexual division of [reproduction] (Chodorow, 1999). Reproductive sexuality is an "indirect consequence" of prenatal sex steroids that, in turn, affect the developing brain to promote sexual behavior where androphilic men and gynephilic women predominate (Bailey et al., 2016, p. 69).

This 'indirect consequence' is curious, but the existence of androphilic males and gynephilic females clarifies that sexual orientation is more dependent on the irreversible effects of early hormones than on the genetic XX/XY sex (Bailey et al., 2016). The early effect does not negate Freud's understanding of sexuality as primarily about bonding ahead of reproduction (Freud, 1966). Sigmund Freud was the first academic to elaborate on the primary function of sexual bonding as the path to intimacy, and its secondary purpose as procreation (Freud, 1966). This elaboration is unsurprising in light of the developmental disconnect between bodily sex (sex) and brain sex (gender) in the trans community discussed later.

Mothering and fathering are tethered to courtship that is tethered to mating behavior, which is, in turn, is tethered to care of dependent offspring. As such, this broader sexuality is relative to reproductive roles, as others have both suggested (Pfaff, 2011; Owen-Blakemore et al., 2009; Bartky, 1999; Buss, 1995) and implied (Reber & Tranel, 2017).

The sexually dimorphic limbic-hypothalamic pathways in the forebrain relate to reproduction and persist unchanged throughout life, although "gonadectomy and steroid replacement have profound effects on cellular levels of sex steroid receptors" (Simerly, 2002, p. 515). For example, one study recorded around 50% of post-operative MtFs experienced a shift in sexual orientation to men (Gooren, 2006), which is perhaps in line with Freud's (1966) theory of sexuality.

Were both Chodorow and Freud correct? In humans, despite the myth-like belief that males seek sexual intimacy over emotional intimacy, and women the reverse, there is evidence women and men exhibited similar valence (Perrin et al., 2011), although the pursuit of the same may differ (Sakata & Crews, 2004). "With the concealment of ovulation in humans, making sex available all the time, the human female succeeded through evolution" to put sex on display and dissociate sex from reproduction, whereby placing feminine beauty on permanent display to help "establish the pair bond and increase and maintain paternal interest and investment in any offspring" (Fathalla, 2015, p. 105). Nevertheless, the physicality of mating per see is not the topic of this article.

Social

Social cognition may have emerged from executive functioning assisted by language. "However, these higher levels operate on previous levels of organization, and should not be seen as independent or conflicting with one another" (Decety & Lamm, 2006, p. 1148).

"Affective sex differences in behavioral and physiological responses ultimately arise from differences in brain activity" (Stevens & Hamann, 2012, p. 1579). Cognitive abilities are notably sexually specific (Ristori, 2020). Social behavior depends on sexually dimorphic circuitry in the cortex and limbic system that processes hormonal, environmental, and experiential information (Newman, 1999). The behaviors relevant to reproduction are enhanced or not differentially between the sexes by this experiential social learning (Sisk, 2016).

As we have seen, subcortical and limbic brain regions are crucial elements in emotional processing (Hahn et al., 2015). The amygdala is a critical element in emotion perception and processing (Pallayova et al., 2019). This region has also been shown to be sexually dimorphic (Pallayova et al., 2019; Lotze et al., 2019; Reber & Tranel, 2017), and its nuclei have connections to other limbic areas (Crestani et al., 2013; Bonelli & Cummings, 2007).

Care of offspring

Behaviors across mammalian species directed toward care of young offspring exhibit striking sex differences (Numan & Insel, 2006). Caregiving by most animals, including humans, is highly sexually dimorphic and provided by mothers. The fact that the most powerful influences on how mothers' mother come from their own experiences growing up and form her infant's reinforcement, serves an important evolutionary role. Considering the amygdala processes negative emotions,

> "a certain amount of heightened arousal and vigilance in this delicate balance is also required for infant care, which involves involve some anxious conduct".
>
> "Synchronous mothers show higher activations of mirror neuron and empathy-related cortical systems, which may point to greater adaptive behaviour."
>
> (Atzil et al., 2011, pp. 2612, 2613).

Behaviors related to reproduction are recognizable in parents as differences in the levels of responses such as sociability, attachment, sentimentality (Stam et al., 2019), aggression (Zell, Krizan, & Teeter, 2015), in defend or befriend (Hoekzema et al., 2015; Sokolowski & Corbin, 2012; McCarthy et al., 2012; Pearson et al., 2009; Zietsch et al., 2008), instinct (Sweatt et al., 2013), and significantly in empathy (Swain et al., 2007).

Behaviors related to reproduction, in which females tend to exhibit superior performance, include verbal and social proficiency, emotion recognition, and empathy (Kret & De Gelder, 2012; Kopsida et al., 2009). Women score higher and favor activity involving relationships, and men favor activity involving things (Zell, Krizan, & Teeter, 2015; Del Guidice et al., 2012).

The association of empathy with parenting is strong. Empathy is "especially relevant to parenting in which infant needs are great, yet most communication is exclusively non-verbal" (Swain et al., 2007, p. 23). Females exhibit elaborate maternal behaviors to ensure survival of their offspring across all mammalian species (Fang et al., 2018). The female's focus in relationships is more interpersonal. Females more than males, are more concerned with others' opinions in social tasks and score higher on attachment, warmth, and empathy (Stam et al., 2019). Estrogen receptors in the heterogeneous MPOA of the hypothalamus are vital mediators of this behavior in mice (Fang et al., 2018). The medial amygdala in mice has been demonstrated in the sexually dimorphic control of parenting behaviors (Chen et al., 2019).

"Sex differences in emotion processing represent some of the most robust sex stereotypes worldwide" (Whittle et al., 2020, p. 319). In humans, differences between the sexes for emotional processing are well-acknowledged (Kreukels & Guillamon, 2016). "Synchronous mothers showed greater activations in the left nucleus accumbens (NAcc) and intrusive mothers exhibited higher activations in the right amygdala. Functional connectivity analysis revealed that among synchronous mothers, left NAcc and right amygdala were functionally correlated with emotion modulation, theory-of-mind, and empathy networks" (Atzil et al., 2011, p. 2603). Hippocampus-lesioned female rhesus monkeys demonstrated significantly higher interest in infants than amygdala-lesioned individuals (Toscano et al., 2009).

Animal and human studies reveal neural and endocrine systems likely account for the development and sensitivity of gendered parental behavior across the lifespan (Champagne & Curley, 2016; Lonstein et al., 2014). The limbic system (the emotional nervous system), specifically the subcortical systems, including the amygdala, hypothalamus, and hippocampus, has been associated with emotion processing and motivation (Tunc et al., 2016). The limbic system zones develop differentially (Zaidi, 2010; Sakata & Crews, 2004; Kruijver et al., 2000) and are stable across the lifespan (Simerly, 2010, 2002; McCarthy & Konkle, 2005). Estrogen sensitivity within the MPOA governs mammalian maternal behavior and is stable across the lifespan (Champagne & Curley, 2016). Arguably, all behaviors related to reproduction and parenting are strongly associated with the RA and parenting roles, but especially empathy and aggression (as defined later).

Empathy

Empathy can be defined as "appropriate perception, experience and response to another's emotion" (Swain et al., 2007, p. 23). It is "the ability to understand and share in the internal states of others" (Christov-Moore et al., 2014, p. 604), and "without confusion between oneself and others" (Decety & Lamm, 2006, p. 146). The significance of empathy is its ability to identify and respond to another's mental state and in the care of offspring; it can respond to infant cues (Schulte-Ruther et al., 2008). Vigil's (2009) introduction of a "framework for understanding phenotypic variation in expressed emotion", presents sex-typical emotive behaviors coevolved "to regulate interpersonal dynamics to enhance social fitness" (Vigil, 2009, pp. 375, 376).

As an ancient biological phenomenon, empathy has both evolutionary and developmental precursors as an instinct involved in the care of offspring. "Evolutionary biologists suggest that empathic helping behavior has evolved because of its contribution to genetic fitness" (Decety & Lamm, 2006, p. 1146). Emotion expression evolved to regulate exploitation and anti-exploitation defences and acquisition of reproductively relevant resources, cooperative resource-acquisition strategies. As a founder of the field of evolutionary psychology, David Buss, expressed:

> Women may express an emotion of sexual desire to deepen a committed relationship in one

> context, or to expropriate a man’s resources.”
>
> “Displays of anger or masculine prowess may signal reciprocal resource capacity, but may also convey to would-be exploiters that one is a poor choice as a potential their victim of exploitation.
>
> (Buss, 2009, p. 392).

Portrayals of females show them as more nurturing and empathetic, and those of males as less emotional and more cognitive. The brain mechanisms mediating empathetic responses are often devoid of cognitive efforts. Moreover, females exhibit higher rates in simple forms of empathy; contagious crying, neonatal imitation, social referencing. The different patterns of empathy remain stable or grow larger with age (Christov-Moore et al., 2014).

The actions of others activate a human mirror system of cortical networks in the self. This automatic response may have adaptive value for individual survival (Decety & Lamm, 2006). Data also suggests these mirror systems are more highly recruited in females (Schulte-Ruther et al., 2008).

An fMRI investigating gender-related differences in brain regions supporting the ability of empathy, reported regions involved in the human mirror neuron system (in particular, the inferior frontal gyrus and Brodmann's Area) are recruited during emotional perspective-taking in both males and females. However, activation is more substantial in females in the right inferior frontal gyrus and right superior temporal sulcus (Schulte-Ruther et al., 2008). Their finding follows previous reports about differences between the sexes in the lateralization of brain functions (see, for example, Cahill et al., 2004).

By directly comparing meta-analytical literature of fMRI and positron emission tomography (PET) neuroimaging for women and men's emotional and neural responses to the same positive and negative stimuli, regional activation differences were noted notably in the amygdala and hippocampal activation. As well, sex differences favoring women were observed for negative emotion, with less activation in men on the same negative stimuli. The converse was noted for both sexes for positive emotion (Stevens & Hamann, 2012). These results parallel findings from the behavioral and psychophysiological literature on substantial sex differences (Yang, Comninos, & Dhillo, 2018; Marwha et al., 2017; Zell, Krizan, & Teeter, 2015; Heberlein et al., 2008; Swain et al., 2007) including response to fear. Across development, females appear to be especially sensitive to perceived interpersonal threats. Numerous studies report sex differences in startle response to social cues that imply the potential of interpersonal threats. Females show greater tendency toward stronger startle potential (McClure et al., 2004).

Generally, contingent behavior is part of social interaction. For example, the first emotive gestures, such as smiling, are produced by human neonates after face-to-face social interaction (Vigil, 2009). Very young infants show contingency between a stimulus and their response and neutral stimulus, such as blowing on baby’s belly each time they jiggle their legs, and positive stimuli, such as the presence of an adult face. Contingent stimuli quickly become a trigger for smiling and cooing.

Contingency is most striking with a face-to-face contact with mother where a baby’s smiling response may occur as early as 3rd day (Watson, 1979). In the first few postpartum weeks, increased activity in mothers' limbic brain regions compared with fathers is observed in response to a baby's cry (Swain, 2007). In relation to mothering, females are better at detecting expressions (LoBue & DeLoache, 2009) and a mother must resonate with the state of her infant's helplessness, meaning she must possess empathy and maternal synchrony (see Atzil et al., 2011).

“Sex typical emotive behaviors would have coevolved to regulate interpersonal dynamics and enhance social fitness” (Vigil, 2009, p. 376). Empathy is an incredibly important emotion in infant nurturant and caregiving (Grabowska, 2017; Swain et al., 2007). The evidence for female advantage in emotional perception and expression (e.g., in recognition of emotions from facial displays) and non-verbal behavior such as smiling and gesturing is consistent (Schulte-Ruther et al., 2008), and the relevance of such an advantage to reproduction and care of offspring is unmistakable.

Several other contributions are consistent with sex differences in empathy, both theoretical (Chodorow, 1999; Gilligan, 1993; Freud, 1966) and empirical (Hines, 2017; Swain et al., 2007; Chapman et al., 2006; Hyde, 2005). Gilligan argued that males and females speak in a different moral voice. Males adopt more selfish-ness, while females embrace more self-less-ness. Gender differences in moral reasoning based on care are higher in women, while men's moral reasoning is more based on justice (Gilligan, 1993). Concern for others guides women's moral compass, while rules guide men's.

In line with innate motherly behavioral tendencies and intuition across the lifespan, newborn girls just a few hours old show more interest in human faces and more sensitivity to tactile, oral, and visual stimuli. This intuition is a basic, immediate, or primitive 'something' that we may see as part of the female self (Gliske, 2019)[2]. Although, there is the caveat that some behavioral differences could be due to differences in the socializing of newborn boys and girls, even within the first few hours after birth (Jones & Lopez, 2014). Nonetheless, considering differences as taxonomic and produced regardless of how a child is raised, nurture may merely influence the average degree of innately focussed difference (Sisk, 2016).

The experience of empathy can be complicated through other social-cognitive factors that modulate it (Decety & Lamm, 2006). Gender and context can modulate empathy. The motivations to avoid empathy can be many, for example, withdrawal from the suffering of others to boost self-protection, material costs, and interference by others. Whereas affixation and social desirability can motivate empathy (see Cromwell et al., 2020; Decety & Lamm, 2006).

Psychiatrist Norman Doidge (2008), neuroscientist Lisa Eliot (2009) and others (Finkel, 2012; McCarthy & Arnold, 2011; Bao & Swaab, 201) argue that the brain itself is neuroplastic, that is, one's experiences can affect one's neural pathways. This is arguably a return of Lamarckism; the idea that experience can influence your genes and those of your offspring (Finkel, 2012). Doidge claims that the only adequate explication of neuroplasticity is that every sustained neural activity changes the brain and mind – including physical, sensory, learning, thinking, imagining, cultural ides, and activities (Doidge, 2008).

Likewise, neural plasticity reveals increased activation of specific cortical regions after several days of empathy training (Singer & Klimecki, 2014). In essence, “empathy plays a central role in moral reasoning, motivates prosocial behaviors, and inhibits aggression toward others” (Decety & Lamm, 2006, p. 1146).

Aggression

The discrepancy in levels of aggression between men and women is striking.

> Men are more likely to show physical aggression. They commit 89% of all murders and 99% of all sexual crimes, while women are more likely to engage in acts of indirect aggression: spreading vicious rumors, gossiping, or fabricating stories about that person.
>
> (Bao & Swaab, 2011, p. 220).

A dominance of testosterone around birth and at about nine weeks of gestation results in masculinization of the brain and genital tract (Zuloaga, 2009; Wizeman et.al., 2001), and males of all ages, including prenatally, have substantially higher T levels than females (Lonstein et al.,

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[2] The publisher has since retracted this paper.

2014). Accordingly, there is strong evidence for sex differences in neural control of the sympatho-adrenal nervous system (Hinojosa-Laborde et al., 1999). At rest, plasma noradrenaline (norepinephrine) levels are consistently higher in females and adrenaline (epinephrine) levels higher in males (Davidson et al., 1984), and men and women react differently to stress, both psychologically and biologically. Findings from neuroimaging record response patterns to stress in the HPA axis and sympathetic nervous system differ markedly between males and females. Female sex hormones lessen the sympatho-adrenal and HPA responsiveness. Sex differences in stress response are portrayed by 'fight-or-flight' in men and 'tend-and-befriend' in women" (Verma et al., 2011).

Gender differences in stress hormones noradrenaline and adrenaline support the view that estrogen reduces sympathetic activity and cortisol and adrenaline secretion. "Control of sympatho-adrenal function is different in females, and responses vary during the menstrual cycles." "The gender differences in noradrenergic neurotransmission may protect females against [hyperactive] sympathetic responses" (Hinojosa-Laborde et al., 1999, p. 122).

In support of the hypothesis that prenatal biology influences postnatal social behavior, fetal testosterone levels in typically developing children measured via amniocentesis and compared to their infant levels (age range 6-9 years), revealed a strong inverse correlation with empathy scores for males (Chapman et al., 2006). Empathy is higher on average in females than in males, and appears to be reduced by fetal testosterone exposure (Hines, 2011). Unsurprisingly, psychopaths exist across all cultures and ethnic groups, and psychopathy occurs more frequently and typically more violently in men (Wynn et al., 2012). Psychopaths have an apparent dysfunction in empathetic response (Ali et al., 2009). Structural and functional magnetic resonance imaging (MRI) has revealed psychopathy and some biological processes in the brain are linked. Core psychopathic features are associated with frontotemporal regions as well as frontotemporal, limbic, paralimbic, and cerebellar structures (Johanson et al., 2020).

Human babies have an extended juvenile period. Care of such dependent offspring requires teamwork from parents that subsumes attachment, suckling, emotional nurturance, and parental sensitivity to danger (Christov-Moore et al., 2014). For primitive fathers, aggressive behavior was a social conduct essential in competition for food, territory, and mating (Gouveia et al., 2019). For contemporary fathers, the care of offspring may also involve physical aggression in the forms of territorial defense and acquisition of resources (Meyer-Bahlburg, 2019), i.e., the view of aggression outlined below. Human babies and their mothers require security and support in resources for many years before they are considered mature, and a partnered father must resonate with the state of his family's needs.

The neural network components that regulate aggressive behavior include the amygdala, the hypothalamus, and the orbitofrontal cortex, all of which have been noted previously as sexually differential (for review, see Gouveia et al., 2019; Unger et al., 2015). As a master regulator, T plays a significant role in the arousal of brain centers involved in aggression and on the development of the muscular system that enables aggression's realization. It acts through the interplay between subcortical structures in the amygdala and the hypothalamus (Unger et al., 2015; Batrinos, 2012). Gonadal steroid levels are increased in a sex-specific manner. During the fourth to the fifth month of pregnancy, a surge of fetal T occurs, lasting a few weeks to reach adult levels that inundate the male brain inducing anatomical and organizational changes (Batrinos, 2012).

Post-natally, T levels peak in boys at 1–3 months of age and decline at six months of age (Kuiri-Hänninen et al., 2014) until puberty. T levels in adult males average 10 - 20 times higher than adult females (AACB, 2020). Higher T levels for women are associated with lower maternal behavior (Smith et al., 2015). Further, male empathy levels appear to be reduced by the higher T exposure in-utero (Hines, 2017), and men with lower levels demonstrate increased parental behavior (Lonstein et al., 2014).

In reply to criticism of her book Testosterone Rex (2017) and her analysis of distorting effects of assumptions about sex differences, Cordelia Fine suggests hundreds of studies mistakenly claim differences in prenatal T hardwire gender identity (Fine, Joel, & Rippon, 2019). That suggestion is in stark contrast to observations that in the final periods of fetal development, the processes of masculinization and defeminization of the hypothalamus are dependent on T secretion (Acevedo-Rodriguez et al. 2018). Similarly, males of all ages have substantially higher T levels than females (AACB, 2020), or that during early pregnancy a surge of fetal T reaching adult levels occurs in the male fetal brain (Batrinos, 2012).

The early effects of T are further highlighted in the study of same-sex (SS) and opposite-sex (OS) twins. OS girls (girls from boy/girl twin sets) showed a more masculine behavior pattern than did SS girls (girls from girl/girl twin sets) with no differences in T levels or pubertal status. The twin study supports T's prenatal levels as higher for OS girls and adds backing for sex differences in aggression overall, similar to congenital adrenal hyperplasia (CAH) girls who show more aggression than non-affected siblings (Cohen-Bendahan et al., 2005). In contrast, studies reveal CAH girls “do not differ from other girls in spatial ability, verbal ability, language lateralization, handedness, or aggression, but may prefer “boy toys” as children and later have decreased sexual interest in men” (Erickson-Schroth, 2013, p. 159).

The spinal nucleus of the bulbocavernosus (SNB) of the lumbar spine in rodents provides an example of a sexually differentiated structure in which T plays a pivotal role. Castration of neonatal male rodents causes the SNB system to die (Zuloaga, 2009).

Across all mammalian species “aggression is a fundamental means to defend territory, compete for mates and food, and protect offspring” (Wong et al., 2016, p. 593). In humans, aggressive behavior is a social conduct typical of ancient Anthropocenes where it was essential in the competition for food, territory, and mating (Gouveia et al., 2019). War in traditional societies required individual striving and centered on reproductively essential resources. It has been argued that lethal conflict arose in the evolutionary context of reproductive striving. Under this view, reproductive competition in warfare can be seen as a significant evolutionary selective force waged in the name of women, bridewealth, revenge, food resources, and territory (Low, 2015).

Boys tend to enact more direct aggression than girls (Card et al., 2008). Aggression, and not empathy, can be formally studied to Ph. D. level in the form of 'War Studies' (Kings College, London). Males score higher than females on measures of aggression (Hyde et al., 2018) and spatial processing [resource attainment] (Reber & Tranel, 2017; Hyde, 2005). Moreover, the difference's magnitude is the largest favoring males in situations with the most danger (Hyde, 2005). In mice, the ventromedial hypothalamus is more responsive to males' presence than to females. This may play a role in male aggression (Wong et al., 2016).

The substantial contemporary differences between a human female and male response in the amygdala to perceived threats of aggression may further support the role of aggression (under another name), or rather its absence, in parenting.

A species' future rests with “the ability of its members to coordinate behavioral responses with physiological processes in response to sexually relevant cues” (Simerly, 2002, p. 508). Within the framework of evolutionary theory, who reproduces best, survives (Low, 2015). Testosterone levels in males of the modern Anthropocene remain high (AACB, 2020), and males are still more likely to exhibit higher levels of visuospatial and navigational skills and direct aggression (Kopsida et al., 2009). Male behavior in modern warfare suggests that the 'band of brothers' even now exists as do the correlations of war as a play for resources, aggressive behavior, and rape (Low, 2015).

Aggression by another name

Following Hare (2017) and Huber and Kravitz (2010), contemporary aggression can be regarded a distant cousin to traditional aggression and can be viewed more helpfully, less aberrant, and more positively as heroics or a competitive spirit related to mate selection, supply and defense of resources, self-defence, and defence of significant others.

A philosophical view of aggression presents masculinity as manifesting itself in cruelty and violence, where no peace negotiations or arguments in favor of tolerance can decrease its intensity (Weigel et al., 2020). Within the 21st-century Anthropocene, such aberrant masculinity is non-essential (Meyer-Bahlburg, 2019). Nonetheless, aggression has not yet evolved out of our species, perhaps simply because aggression is nowadays aligned more positively with 'heroics, a competitive spirit related to mate selection, supply and defence of resources' etcetera as Huber and Kravitz (2010) proposed. While the defining characteristic of the human domestication syndrome is dampened reactive aggression, i.e., a decrease in physical aggression and fear (Hare, 2017), unfortunately, as with all human behaviors, some individuals and societies misuse their natural tendencies.

A contemporary notion of aggression understands it as a competitive spirit alongside a willingness to mount violent defences against outsiders signifying a kind of natural selection for friendliness and characteristics that enhance mating ability, survival, and reproductive success (Sunstein, 2020).

In sum

Prenatal development is arguably a period when the fundamentals of gender as cognitions relative to reproduction presented herein are laid down. These cognitions are specifically tethered to reproduction and care of offspring. Reproduction of our species demands differentiation in the physical and psychobiological care of offspring. After heterosexuality, the two most notable differences in cognitive behaviors discussed here occur concerning offspring's care as empathy and aggression.

Post adolescence, sexually dimorphic courtship is tethered to sexually dimorphic mating behavior, which is tethered to sexually dimorphic Mothering and Fathering, which is, in turn, tethered to dimorphic roles in the care of offspring. These differential networks are presented here, as reflected in the distinctive behaviors relevant to reproduction stemming from the RA. The higher levels of empathy shown by females are likely the 'why women mother' that Chodorow was missing (Chodorow, 1999), whereas fathers predominate in other parental areas.

This article presents the emergence of a subconscious awareness of this reproductive axis as gender. The strength of any sexual dimorphisms related to gender incongruence may not be homogenous and may also be located in one, some, or all RA regions along a spectrum (see later).

4. EXEGESIS FROM SEX / GENDER INCONGRUENCE

As a reproductive axis must exist in trans and non-heterosexual individuals, it would be remiss or deemed transphobic to focus on gender identity without engaging the research into sex/gender diverse communities.

Timing is everything

Neurogenesis and Corticogenesis

Neurogenesis is sequential, and corticogenesis, in particular, are time-sensitive neural developments.

The sequential birth of different cell types is known as 'temporal patterning,' an evolutionary strategy generating neuronal diversity. “The cerebral cortex is intimately linked with temporal patterning” (Rossi et al., 2017, p. 7). The early brain develops sequentially. Two to three weeks after conception, folding and fusion of ectoderm creates the primitive neural tube of the CNS (Marsh et al., 2008).

At the end of the seventh gestational week, when the gonads are developed, and sex is determined, other parts of the reproductive system are still bipotential (Tasopoulos, 2018). The head is almost as large as the rest of the embryo's body by the eighth week (OpenStax, 2016), and stem cells differentiate into sensorimotor regions of the cortex and significant midbrain components regions and the spinal column for division into cortical and subcortical neurons (Marsh et al., 2008). For example, DTI of 13 week old post-mortem fetal brains reveals limbic neural tracts as major tracts (Huang et al., 2009).

By the tenth week, the fetal stage begins when a developing embryo establishes the rudimentary structures of all of its other organs and tissues (Stiles & Jernigan, 2010). During the perinatal period, fetal hormones activate and organize the neural substrate (Menger et al., 2010). Perinatal testosterone levels organize fetal male and female brains differently (Jones & Lopez, 2014).

Notably, the fetus is anatomically organized, differentiated, and producing sex hormones before neurogenesis is complete, and these same hormones exert their activational effects on the developing brain (Luine, 2014; Bao & Swaab, 2011; Savic, Garcia-Falgueras, & Swaab, 2010). This temporal and physical displacement of body and brain developmental processes means it is possible for the "sex of the genitalia" and "brain gender identity and sexual orientation" to become discordant (Tasopoulos, 2018) or incongruent (Roselli, 2018). In other words, the development of body and brain phenotypes are temporally displaced; specifically, (body) sex is developed before the CNS development is complete (Swaab, 2007).

The trans community

The reproductive axis is common to cis and trans identities, making the trans community another candidate in examining subsystems as the source of gender identity.

Research has presented a huge collection of genetic and hormonal factors that may lead to gender issues (Swaab & Garcia-Falgueras, 2009), though the word 'problems' here is unfortunate. Nonetheless, the trans community's origins and non-heterosexuality are as yet far from proven (Roselli, 2018).

By age two to three, most children have an awareness of their gender (Ahmed et al., 2004), and most without issue. A very few, on the other hand, feel a sense of unease. We now refer to distress resulting from this unease as gender dysphoria (GD) (Sánchez & Vilain, 2013). Late-onset gender dysphoric individuals whose earliest memories are filled with similar unease yet not acted upon until later adulthood mechanisms come into play. The mechanism here is also unclear.

What is most relevant to our hypothesis is not what causes sex and gender diversity, but specifically, what and where is it trans people of all ages feel is inconsistent with their biological sex? What is it many children identify as their gender as early as age two (Zucker, Bradley, & Sanikhani, 1997), or age three (Olson & Gülgöz, 2018; Hewitt et al., 2012)? If there is no internal biological locus for gender identity, what is it very young and persisting adult trans individuals feel inconsistent with their bodily sex? What the dysphoria apprehended by late-onset individuals?

If gender is an entirely social construct, all hair, and makeup, as has been implied (Rippon, 2017; Butler, 1990), age six months to five years seems insufficient time to learn the political and socio-cultural structures of gender without some prior form of influence, namely in utero.

Across studies in trans populations, hints of a developmental disconnect between bodily sex (sex) and brain sex (gender) are apparent. This disconnect led us to question what and where is it trans individuals feel is inconsistent with their biological sex? How can this disconnect exist before very young trans children absorb cultural and social influences? Intense pre-pubescent dysphoria persisting into adulthood is an essential DSM V requirement for the diagnosis of GD. Our hypothesis speaks directly to early-onset individuals who have not had sufficient time to absorb and learn the nuances or politics of sex and gender so often presented as the sole gender source.

A brief outline of research into this broad topic provides some evidence for cause and or consequence of gender incongruence, including genes, epigenetics (Fernandez et al., 2020, 2018; Arnold, 2017; McCarthy & Arnold, 2011; Ngun et al., 2011; Jones & Lopez, 2014), hormones, Menger et al., 2010; McCarthy, De Vries, & Forger, 2017), neuroanatomy and function (Beking et al., 2020; Mueller et al., 2017; Kreukels & Guillamon, 2016; Burke, Manzouri, & Savic, 2017; Luders et al., 2009; Rametti et al., 2011; Savic & Arver, 2011; Smith et al., 2015), and environment (Tozzi et al., 2019; Gräff et al., 2011). As yet, none are conclusive.

However, it does appear that differences in relation to body sex, gender identity, and sexual orientation, differ neurologically, both structurally and functionally, indicating these traits develop independently (Roselli, 2018). Trans studies alone do not locate gender as such; nonetheless, it highlights the multifactorial basis for gender identity and how the effect of various factors could be a part of the gender network within the regions of the reproductive axis. For example, estrogen's actions on the developing hippocampus, cortex, cerebellum, hypothalamus, and amygdala, are generally permanent and range from the establishment of dimorphic sex differences to generalized effects (Fernandez et al., 2019). As we saw, T's actions "in the final periods of fetal development are fundamental for the processes of masculinization and defeminization of the hypothalamus" (Acevedo-Rodriguez et al. 2018, p. 11). T plays a significant role in the brain centers' arousal of behavioral manifestations (Unger et al., 2015). Over time, T levels imply it can be considered a "trait" (Smith et al., 2012, p. 12).

Trans dimorphisms in brief

"The theory of the origin of transsexuality is based on the fact that the differentiation of sexual organs appears well before the sexual differentiation of the brain" (Bao & Swaab, 2011, p. 217). Considering this temporal displacement, the hypothalamus has been heavily implicated in the origins of trans identities. This implication is supported by sex reversal in the BSTc and INAH3 regions of the hypothalamus in trnas individuals (Smith et al., 2015; Bao & Swaab, 2011). However, this factor alone cannot be used for early diagnosis of transsexuality because sex difference in BSTc volume is not apparent until early adulthood (Bao & Swaab, 2011), making it possible that the differences are not a cause of transsexuality but rather a result (Chung, De Vries, & Swaab, 2002). Furthermore, the effects of oestrogen or androgen treatments for the changes in the hypothalamus of transsexuals cannot be discounted (Guillamon, Junque, & Gómez-Gil, 2016; Pol et al., 2006).

Understanding the biology of gender dysphoria requires consideration of other sexually dimorphic cerebral networks to investigate networks processing own body perception (Savic & Arver, 2011).

Body perception

Disruption of the genetic programming of frontoparietal and limbic circuitry may be a prime mechanism underlying a variety of social disorders such as schizophrenia, and attention deficit hyperactivity disorder (João & Filgueiras, 2018; Sokolowski & Corbin, 2012; Jia et al., 2009) and autism spectrum disorder in the trans community (Hines, 2011; De Vries et al., 2010). It appears trans individuals are "unable to incorporate typical body characteristics of their gender assigned at birth into their own body representation in the brain" (Fisher et al., 2020, p. 2).

Frontoparietal disconnection has been implicated in gender incongruence and dysphoria (Feusner et al., 2017; Burke, et al., 2017). GD individuals differ with respect to connectivity within networks involved in self-perception and own-body identification (Feusner et al., 2017).

Again though, and following on from the understanding that any distinct region of the CNS is unlikely to serve as the entire neurobiological location for gender in the cisgendered, the biology of gender incongruence with or without dysphoria would require consideration of other critical regions.

Cortex - PFC

In early-onset trans individuals, gross brain morphology in various areas such as cortical thickness, white matter microstructures, ERα, and ERβ, suggests their atypical or multifaceted brain sex development (Fernandez et al., 2018; Kreukels & Guillamon, 2016). Hormone treatment is further associated with changes in cortical thickness and cortical and subcortical volume (Kreukels & Guillamon, 2016). Further studies report different cerebral connectivity profiles of female-to-male (FtM) and male-to-female (MtF) subjects compared to cisgender controls (Kreukels & Guillamon, 2016).

Hippocampus

Hormone naïve FtM trans individuals follow natal female hippocampal differences (Manzouri, Kosidou, & Savic, 2017). In trans individuals, the amygdala and hippocampus develop with size and neuron numbers closer to the desired rather than natal sex (Smith et al., 2015).

Amygdala

Hormone naïve FtM subjects display female type connections within the amygdala (Manzouri, Kosidou, & Savic, 2017). Amygdala volume in MtF subjects is consistent with their sex at birth, not their gender identity (Mueller et al., 2017).

Hypothalamus

The bed nucleus of the stria terminalis (BNST), located in the basal forebrain, connects the amygdala, hippocampus, hypothalamic, and brainstem nuclei associated with autonomic and neuroendocrine functions. The INAH is presumed a key component in controlling autonomic, neuroendocrine, and behavioral responses - the social behavioral network (Crestani et al., 2013). Trans studies have reported sex differences in hypothalamic nuclei's structural and functional differences (Bao & Swaab, 2011). Subdivisions of the hypothalamus related to various sexual orientation aspects match their identified gender identity (Swaab & Garcia-Falgueras, 2009).

Connectivity / Connectome

In a review of in vivo brain imaging covering the entire structural and functional literature in people with gender incongruence, structural and connectivity differences between transgender and cisgender subjects have been demonstrated. These include microstructural differences in gray matter and white matter and cerebral connectivity profiles (Kreukels & Guillamon, 2016). Other authors conclude that most local physiological aspects of gender identity in trans individuals have undergone a biological transition (Hahn et al., 2015).

The genetic milieu contributing to gender identity may be completely different from one

> individual to the next. While, in some individuals, a single genetic variant may be sufficient to result in gender dysphoria, it does not follow that that variant would be necessary or sufficient to cause gender dysphoria in the population at large.
>
> (Theisen et al., 2019, p. 8).

As was noted previously, the strength of sexual dimorphism in the cisgendered is likely homogenous across all of the RA, while the pattern for causes of incongruence in the trans community suggests sexual dimorphisms may be heterogenous, i.e., any or many, leading to many phenotypes across a spectrum. What more, the bio-psycho-social approach to the study of trans individuals is again highlighted because the reasons any one individual identifies as trans are likely numerous (Erickson-Schroth, 2013). While causes for gender incongruence may depend on a milieu of origins, we are left to acknowledge current theories involve regions of the RA, specifically the limbic system.

There remain confounding issues in trans research, and trans studies have faced many confounding issues (Fine, 2020; Hyde, 2005). Confounds include - the scant number of MRI studies; a mix non-heterosexual and heterosexual subjects; small numbers of age-matched studies; a scarcity of early-onset studies compared to later onset where no allowance is made for the variety of years already lived; relatedly the use of post-mortem studies, and age-unmatched post mortem studies. Any trans research that does not incorporate these appropriate exclusion and inclusion criteria make it very difficult to establish cause and effect.

It would seem imperative that inclusion criteria of early age of onset and pre-treatment (hormone naïve) are particularly crucial in identity studies, so the studies reviewed here all qualify for these inclusion criteria. The research outcomes presented here highlight the different biology of gender, its similar location within the reproductive axis to the cisgendered, and its disconnect in the trans community.

While many similar structures have been implicated in trans and non-heterosexual subjects, most non-heterosexuals are not trans, and some trans individuals are heterosexual. Non-cisgender individuals are less likely to reproduce as much as the cisgender population (Swaab & Garcia, 2009) and therefore tend more toward reproductive isolation despite their permanent place in evolution (Rice, Friberg, & Gavrilets, 2012).

The pattern for the causes of gender incongruence suggests they may be any or many, leading to many phenotypes. For example, WM studies suggest that MtFs do not show a simple feminization of their brains; instead, they present a complex picture of feminized and incompletely masculinized structures (Guillamon, Junque, & Gómez-Gil, 2016). While causes may depend on this milieu of origins, we are left to acknowledge current cisgender and trans theories involving regions of the RA, specifically the limbic system. These distinctions provide further support for the probability that the RA's physiological regions form a neural location for gender, physically and temporally separate to body sex, at least in part.

Persisters and Desisters.

While debates about the validity of labelling children as persisters and desisters have been prominent (Temple-Newhook et al., 2018; Zucker, 2018), this article has asked if there is no internal locus for gender identity, then what is it very young and persisting adult trans individuals feel is inconsistent with their bodily sex?

Permanent morphological changes in the CNS may occur due to exposure to steroid hormones at approximately the time of birth. Overt genital anatomy “will radically shape the child's social environment” (Zuloaga et al., 2009, p. 352), or earlier if the sex of a child is known antenatally.

Most children express their sense of gender and correctly label others by age two or three (Ahmed et al., 2004; Leinbach & Fagot, 1986). Pre-puberty (ages 3-12) is arguably a time when most gender opposite children, with or without any dysphoria, have not necessarily had sufficient time to comprehend their dissonance nor any competing script to how they feel and behave, and especially in the very young.

“Pubertal hormones likely contribute to the dramatic changes in behavior and brain structure in human adolescents.” The concurrent “emergence of sex differences in mood and anxiety disorders during adolescence may relate to sex differences in brain development or to sex differences in pubertal hormones” (Marsh et al., 2008, p. 7). On the other hand, children experiencing GD pre- and post-puberty (persisters) do not appear to be affected by the usual sex hormone activations of puberty (Guillamon, Junque, & Gómez-Gil, 2016).

Many early-onset trans individuals, anywhere in the order of 70-98% (Steensma et al., 2011), may desist both due to the resolution of difficulties other than sexual dimorphism and sex hormone changes in puberty (Gliske, 2019). Others claim “It would be surprising if the large orientation differences in childhood gender nonconformity disappeared without a trace by adulthood” (Bailey et al., 2016, p. 58). For example, childhood occupational and recreational interests appear to linger into adulthood (Bailey et al., 2016).

In the less susceptible pubescent children who 'desist,' the activational effects of adolescent sex hormones and environment might play a significant role in their mindset (Guillamon, Junque, & Gómez-Gil, 2016). Synaptic plasticity (Tozzi et al. 2019; Gräff et al. 2011) may also account for how changes in sex hormones in aging contribute to late-onset dysphoria.

Crucially, the percentage of 'desisters' does not number 100%. Furthermore, the notional merging into sex/gender of otherwise distinct sex and gender, and the claims that gender is a social construct, seem to ignore both the very young pre-pubescent trans children who persist post-puberty as well as individuals who experience, re-experience or relive a gender opposite to their bodily sex later in life.

This current paper has focused on the specific cognitions driven by reproductive networks in the RA as the foundation of gender identity. Our observation is that the causes of gender incongruence are similarly the source of congruent cognitive differences in the cisgender population, highlighting the similar biological origins of gender identity.

DISCUSSION

It is challenging to “unravel the function of neural circuitry in general…This makes it tricky to link relatively consistent sex differences in brain structure to more fickle sex differences in brain function” (de Vries & Södersten, 2009. p. 589) . When differences are context-dependent across domains, it becomes even more complicated unravelling sex and gender discussions (Del Giudice et al., 2012), and more so when it may not be acted upon until adolescent hormones kick in (Jones & Lopez, 2014).

As we and others have mentioned, biology and culture work hand in hand, and it is very difficult to impossible to separate the influences of one from the other (Joel, Garcia-Falgueras, & Swaab, 2020; Fine, Joel & Rippon, 2019). Regardless, some authors have not made what we consider a meaningful distinction between general cognitive behaviors and those relative to reproduction, choosing instead to consider behaviors related to 'reproduction' as physical and nothing more, seemingly bypassing limbic system function relative to reproduction. “From flies to mice and rats, sex behavior is controlled to match the reproductive capacity of each individual and the availability of resources” (Lenschow & Lima, 2020, p. 164).

If we separate general behavior from cognitive behavior relevant to reproduction and maintain the RA, specifically the limbic system, as the center of gender identity relative to reproduction, then pubescent children who consistently, persistently, and insistently (Olson & Gülgöz, 2018) maintain a gender opposite to that assigned at birth, and whose later reproductive behavior is not always conventional for their sex, arguably make the notion of gender as a singular social category of sex/gender insufficient.

Accepting sexuality as the global term concerning reproduction presented earlier and the differences in courtship, aggression, empathy, and care of offspring as essential to reproduction, the significance of the RA, and especially the limbic system, to gender identity, becomes more evident. While there will be some overlap in behaviors related to reproduction, and gender is not categorical, they are sufficiently polarized that average differences remain significant and relevant (McCarthy, De Vries, & Forger, 2017; Carothers & Reiss, 2013).

Borrowing from McCarthy, De Vries, and Forger (2017), we can say a handful of sex differences in the CNS can be linked to differences in sexual (physical) behavior. Of most other (cognitive) sex differences, we can ask would dimorphic differences give males and females any advantage in terms of function. Humanity endures through a cycle of reproduction and survival, and the claim that human behavior is, therefore, dependent on associated physical and cognitive behaviors is worthy of examination. Such an examination may also answer the hypothetical question why we would have a gender.

This article presented the RA as the location of gender. The interconnected RA networks control both the physical and cognitive behaviors relevant to reproduction. Despite the mosaic of other cognitive behaviors, gender identity has been presented as differential and tethered to behavior relevant to the RA, hardwired into the subsystems of the cortex and limbic system, and separate to higher-order executive functions regulated by gray and white matter.

Fronto-parietal connectivity theories of identity suggest connectivity between inter and intra connectivity networks is different in trans males than in cisgender males, i.e., there is an altered connectivity phenotype or disconnectivity in parietal regions (Uribe et al., 2020). The interaction between neurological networks is reportedly a foundation to building a gendered self, particularly between the right and left frontoparietal regions (Uribe et al., 2020). The location of gender presented more broadly herein, is in line with body perception network models. Body perception models present its fixed neurophysiological signature related to interconnected networks in the frontoparietal cortex, amygdala, hypothalamus, i.e., in the whole RA. The behaviors associated with the RA networks are presented as moderately focussed or canalized towards male and female endpoints. This awareness is present in both cis and trans gendered individuals and is otherwise known as body perception.

CONCLUSION

This project evolved out of a desire to answer the question; how is it that dimorphic bodily sex creates two distinctly different reproductive systems, yet allows for a human mosaic of cognitions that are surprisingly similar yet flexible (Fine, 2020)? To begin our research, we turned the question upside down and asked; considering we are not a heteromorphic species and only females endure the physicality of childbirth, and males do not, why wouldn't there be differences in innate cognitions relative to the differences in the reproductive burden which are adaptive? This paper does not propose T or estrogen hardwire gender identity per se; rather, reproductive hormones hardwire the inclination toward male or female cognitions relative to reproduction, which contribute to gender identity.

To this end, this review carried out four primary goals:

(1) split the behavioral domain of the general cognitive mosaic of functions from those cognitions

explicitly related to reproduction.

(2) examined the possible location of biological origins and for those cognitions and whether they are dimorphic.

(3) presented dimorphic neural regions and their associated behaviors as the source of gender.

(4) examined the same regions in the trans community for support or otherwise for the biological source of gender.

Under the assumption that there are structural and functional differences between the sexes, our goal was to reason backward to see if and what behavioral differences mattered to reproduction, i.e., species survival. Then by asking what it is very young trans children identify as opposing their sex assigned at birth, we examined similar regions to the cisgender community.

If evolution has selected sex-specific organization relevant to reproductive fitness, then neural circuitry will also be a function of sex (Sisk, 2016). Yet when it comes to emotions, even Darwin was puzzled. Emotional differences have still to be fully understood from an evolutionary perspective, nonetheless, according to the theory of phenotypic variation for expressed emotion, sex-typical emotive behaviors co-evolved to “regulate interpersonal dynamics that enhance social fitness” (Vigil, 2009, p. 376).

“The adaptive significance of affective responses (e.g., emotions, dispositions, moods) lies in their expression and that affect behaviors function to systematically motivate other people to respond to the signaller in ways that enhance the signaller’s fitness” (Vigil, 2009, p. 376). The differential in reproductive burden indeed necessitates differences in effective responses that are characterized in gender differences.

The self-domestication hypothesis claims social skills evolved when natural selection favored increased self-control and group pro-sociality over aggression in late human evolution (Green & Spikins, 2020; Hare, 2017). Accordingly, we can add that effective responses such as empathy and contemporary aggression (a competitive spirit in combination with defense of resources, self-defence, and defence of significant others), as presented herein, are adaptive behaviors in that they aide survival of offspring. These gender differences become apparent in the biology of the reproductive axis. And so, the essence of gender is our subconscious awareness of our reproductive Id or archetype.

All factors considered, we know that sex-related brain structures in the RA are at least partly distinguished pre- and post-natally, so biology drives this part of one's self-concept (recognized in Freudian psychoanalysis as the "Id"), while the other is socially constructed (recognized in Freudian terms as the 'Superego'). In Jungian psychoanalysis, the "archetype" is where latent instinctual energies await development and expression.

The framework of evidence for sex vs. gender in the reproductive axis and the effects of incongruence in trans healthy subjects, has not been presented previously. The evidence reviewed in the cis and trans communities points to the RA's key role in coding for gender identity.

The differential organization of the fetus and its brain must be managed or directed one way or another, or as Purves implied - bodily processes must be linked to neural differentiation (Purves, 1989). Because of temporal linking and the consecutive organization of body and brain, the two processes can be influenced independently, resulting in their miss-alignment or incongruence (Bao & Swaab, 2011; Savic, Garcia-Falgueras, & Swaab, 2010).

With a biology for gender, the ability to study it further could lie hand in hand with its neurological location. Variation in the linkage of sex and gender implied by Purves (1989) could further provide a unified explanation for conventional and unconventional human diversity alike. Variation in this linkage could be significant to a causal explanation for gender diversity within linked spectrums.

A physiological location for gender distinct from sex could help advance the apolitical understanding of unconventional or incongruent gender identities. As mentioned, sexual dimorphisms may be located anywhere along a spectrum. It is clear, for example, that spectra distribute sexual orientation (Savin-Williams, 2014) from attraction to the opposite sex, the same sex, both, or none, and sex differentiation is “typically associated with a spectrum of external genital development” (Lee et al., 2016, p, 164) accounting for disorders of sexual development (García-Acero et al., 2020) or the reported 2% frequency of intersex individuals in humans (Blackless et al., 2000), while others classify intersex as a phenotype, not a genotype (Wizeman & Pardue, 2001). Borrowing from Meyer-Bahlburg (2019), while it may be recognized XX / XY genetic binaries canalize differentiated taxons, the existence of intersex bodies, although rare, testifies to the overlapping of canalized bodily sex (García-Acero et al., 2020; Swaab & Bao, 2016; Ainsworth, 2015). O'Hanlan, Gordon, and Sullivan (2018) present an example of over 450 quadrillion possibilities of dimorphism.

Combined with our unique human consciousness and self-awareness, essential cognitive and emotional differences described herein credibly make for our perpetual sense of gender, from which men and women adopt a gender role identity to express gender via individual gendered displays in their social world (West & Zimmerman, 2009).

In conclusion, we propose that gender identity is the innate sense of ourselves arising out of the interlinked networks of the reproductive axis. This network could be represented by the pseudo-equation: gender identity = gonads + cortex + prefrontal cortex + pituitary + limbic system (hippocampus, amygdala, hypothalamus). This “equation” does not represent how the various elements are not necessarily additive, and are not necessarily equally weighted. It does represent the multifaceted components involved in gender identity as well as in gender incongruence.

Gender identity is therefore presented as innate and aligned with our future reproductive roles as mothers and fathers. Nevertheless, because of the temporal nature of this linking and the consecutive organization of body and brain, the two processes can be influenced independently. In a tiny percentage of people, 0.5–1.4% of natal males and 0.2–0.3% of natal females (Theisen et al., 2019), this alignment is unconventional.

Postscript -The end of Gender?

> “At the beginning of the 21st century, [however], posthumanist and transhumanist discourses about using technologies to intentionally transcend the limitations of the human body began to address the transcending of gender.”
>
> (Dvorsky, & Hughes, 2008, p. 7).

McCarthy and Arnold (2011) proposed X and Y genes are the factors at the root of all differences in the human phenotype, yet, some predict 'gender' as we know it may cease to exist in the distant future. Indeed the concept of "gender isn't what it used to be" (see Thurer, 2005). That premise is based initially on social construction theory, with gender regarded as forming solely under the influence of parenting and society.

Under this radical social construction of gender, it is indeed feasible differences in gendered behaviour could be erased (see Woodhill & Samuels, 2004). However, the social construction of gender does not explain the innate differences between males and females presented herein.

Evolution as understood by Darwin, evolutionary psychology, and human behavioral ecology (where genes and culture interact slowly over millennia), may be outpaced by technology, whereby alteration in the ecology of gender may become feasible. The role of reproductive hormones in uterine development also spawned the possibility of psychopharmacology that may increase control over gender emotions and cognitions, for example, suppressing the male propensity for violence (Dvorsky, & Hughes, 2008).

Considering the relationship between parenting and technology has always existed, and the exponential rate of technological advance we are now experiencing (Krusnick, 2018), along with our Lamarckan ability to adapt phenotypically, microbiologists have discovered ways to interfere with the chromosomes of plants, animals, and humans under the aegis of genetic engineering.

> Postgender technologies may put an end to static biological and sexual self-identification, allowing individuals to decide for themselves which biological and psychological gender traits they wish to keep or reject
>
> (Dvorsky, & Hughes, 2008).

Molecular biologist Elizabeth Finkel has asked what have we learned from all this (Finkel, 2012)? Alongside the momentum in neurotechnology, biotechnology, and reproductive technologies, we may be moving into a post-Darwinian, post-human era (Killeen, 2019; Dvorsky & Jones, 2008) and on to the slow erosion of sex and gender as binaries.

Though that does seem a long bow to draw, Dvorsky and Hughes assert that “Today's transgender movement is a roiling, radical critique of the limits of gender roles, with folks living in totally new categories, such as non-op transsexual, TG butch, femme queen, cross-dresser, third gender, drag king or queen and transboi.” These authors go on to present the focus on a landscape of gender diversity is somewhat more at the level of ideology, psychology, and culture that lack praxis in the real world.

Feminist degendering theories (Lorber, 2000) theoretically destabilise the fixed and biological root of sexual dimorphism (Nicholas, 2012, p. 1). Feminist degendering wishes to challenge “simplistic divisions of nature/culture and sex/gender” to eradicate gender difference (Nicholas, 2012, p. 2).

The call to free ourselves from the categories of gender presents a problem. Considering the broader acceptance of gender as a spectrum, there can be no end to the terminology of identity as foreshadowed above. In contrast to the debates between radical social constructionism and radical gender essentialism, we see a resolution in the balanced bio-psycho-social model. We can speculate via the notion of canalization as presented herein; there is sufficient overlap in the human phenotype to restrict the free-for-all labelling to a few polarized labels, such as the LGBTQI currently in use (Woodhill & Samuels, in preparation).

This current paper maintains the inseparability of spectrums for sex, gender, sexual orientation, and gender roles (Woodhill & Samuels, (in preparation). However, rather than reifying difference, this paper reduces it to that of reproduction behaviors, leaving the remainder of behaviour available in sufficient quantities to both sexes without any imposed hierarchy or exclusion.

In response to the clarion feminist cry that dyadic gender roles and sexual dimorphisms are to the detriment of individuals, we maintain reproductive gender as innate and have always seen this cry more as a mistaken attempt to adopt an androgynous personality, no matter how one identifies (Woodhill & Samuels, in review).

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Woodhill, B: Conceptualization; Project administration; Resources; Software; Writing - original draft & editing; Writing - review & editing.

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