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A new theory of gender dysphoria incorporating the distress, social behavioral, and body-ownership networks

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Abstract

When postmortem studies related to transgender individuals were first published, little was known about the function of the various identified nuclei. Now, over two decades later, significant progress has been made associating function with specific brain regions, as well as in identifying networks associated with groups of behaviors. However, much of this progress has not been integrated into the general conceptualization of gender dysphoria in humans. We hypothesize that in individuals with gender dysphoria, the aspects of chronic distress, gender atypical behavior, and incongruence between perception of gender identity and external primary sex characteristics are all directly related to functional differences in associated brain networks. We evaluated previously published neuroscience data related to these aspects and the associated functional networks, along with other relevant information. We find that the brain networks that give individuals their ownership of body parts, that influence gender typical behavior, and that are involved in chronic distress are different in individuals with and without gender dysphoria, leading to a new theory—that gender dysphoria is a sensory perception condition, an alteration in sense of gender influenced by the reflexive behavioral responses associated with each of these networks. This theory builds upon previous work that supports the relevance of the body ownership network and that questions the relevance of cerebral sexual dimorphism in regards to gender dysphoria. However, our theory uses a hierarchical executive function model to incorporate multiple reflexive factors (body ownership, gender (a)typical behavior, and chronic distress) with the cognitive, reflective process of gender identity.

Significance

Our new model highlights connections between multiple dimensions of gender dysphoria and behavioral neuroscience data, explaining the experience of gender dysphoria using relevant neural substrates and networks. This biology/symptom-based approach provides an updated theory of gender dysphoria, fostering new hypotheses to advance basic understanding of the condition.

Introduction

Just over 20 years ago, a publication reported the first observed neurobiological difference between cisgender and transgender individuals (Zhou et al., 1995). In particular, the bed nucleus of the stria terminalis (BNST) was found to have a smaller average size in male-to-female (MtF) transgender individuals, with a size more similar to that of an average cisgender female than cisgender male. For context, see the accompanying commentary (Breedlove, 1995). More succinctly, Breedlove was described in a New York Times article as expressing that the "function of the bed nucleus in human behavior, sexual or otherwise, remained 'a complete black box'" (Angier, 1995). Interpretation of the BNST results at that time thus focused on the size difference rather than the function. As MtF transgender individuals had a size more similar to their desired gender than assigned gender, these data supported the theory that distress in gender dysphoria was due to an anatomical incongruence between brain and body sex. The

incongruence was then specifically stated to be that transgender individuals have brain sex opposite to their gender assigned at birth. For clarity, we will refer to this theory as the opposite brain sex theory, which is in the category of theories involving atypical cerebral sexual differentiation.

Today, the BNST is no longer a black box but has several identified functions. For example, the BNST is a key component of the fear/distress network (Lebow and Chen, 2016; Tillman et al., 2018). Although chronic distress is a defining characteristic of gender dysphoria, the connection between the functional role of the BNST and its association with gender dysphoria appears to have received little consideration. In contrast, the connection between anatomical changes in the body ownership network and gender dysphoria has been a focus of several recent studies (e.g., (Burke et al., 2017b; Manzouri et al., 2017; Manzouri and Savic, 2019)). The results on both the distress and body ownership networks suggest a theory in which each aspect of gender dysphoria is explained by the functional significance of known neuroanatomical differences. Specifically, we hypothesized that in individuals with gender dysphoria, the aspects of chronic distress, gender atypical behavior, and incongruence between perception of gender identity and body sex are all directly related to the functional implications of the underlying differences in neurobiology. We considered the plausibility of this hypothesis by examining published literature regarding the function and behavioral roles of neuronal substrates found to be different in transgender individuals.

After considering this hypothesis, we present a new theory of gender dysphoria, consistent with the latest neuroscience data, that stands in contrast to the common opposite brain sex theory and builds upon the work relating body perception with gender dysphoria (Burke et al., 2017b; Manzouri et al., 2017; Manzouri and Savic, 2019). We denote this new theory the multisense theory of gender dysphoria. This new theory focuses on function, including sense of

gender and its inputs, rather than male/female dichotomy in anatomical size and shape (the focus of the opposite brain sex theory). For clarity, in this document we use "sense of gender" to refer to the emergent sense arising from the function of multiple networks, and "brain sex" to refer to anatomical characteristics of the brain relative to male/female dichotomy. We also use the term "transgender" throughout this manuscript, though recognize that some references instead use the word transsexual to refer to the same concept. We observe, based on previously published data, that the primary mechanism behind the experience of gender dysphoria appears not to be that the anatomical brain sex is opposite to gender assigned at birth. Instead, we propose that systemic changes in functional networks, specifically the distress, social behavioral and body-ownership networks, result in the incongruence between sense of gender and gender assigned at birth.

Background Material

The new theory is rooted in published neuroscience data related to gender dysphoria and behavioral roles of the associated neuronal substrates. Most of this information has become available within the last 20 years, with more than half of the cited references being published within the last six years. We organized available information around three key dimensions of gender dysphoria, consistent with the Diagnostic and Statistical Manual of Mental Disorders, version five (DSM-V). Specifically, the three dimensions were 1) chronic distress, 2) gender non-conformity, and 3) incongruence between perception of gender identity and body sex. In this categorization, the desire to become a gender other than assigned-gender is viewed as a resultant effect of these three dimensions. The presence of dimensions (2) and/or (3), without severe distress (dimension 1), does not constitute gender dysphoria according to the DSM-V.

Dimension 1: Chronic distress

The key neuronal substrate for processing distress is the central extended amygdala, which includes the BNST and central medial amygdala. The extended amygdala is implicated in psychiatric conditions including extended duration fear states such as chronic dysphoria (Lebow and Chen, 2016). The BNST is also a component of several important networks, including the social behavioral network (Newman, 1999), the mesolimbic reward system (O'Connell and Hofmann, 2011), the hypothalamic-pituitary-adrenal (HPA) axis (related to acute stress) (Zhu et al., 2014), and the sleep/wake system (Saper et al., 2005b, 2005a). Altered size of the BNST was the first noted anatomical change associated within MtF transgender individuals (Zhou et al., 1995). The BNST is also part of a larger distress-processing network, involving the periaqueductal gray, anterior insula, dorsolateral prefrontal cortex, mid-cingulate cortex, and orbitofrontal cortex (Tillman et al., 2018). Two additional nodes of the distress network, the anterior insula and orbitofrontal cortex, have also been found to be altered in transgender individuals (Manzouri et al., 2017; Zubiaurre-Elorza et al., 2012); see Fig. 1.

Dimension 2: Gender non-conformity

Most behaviors associated with being typical of a given gender are under control of the social behavioral network. Categories of behaviors typically associated with this network include parental, sexual, and aggressive behaviors (Newman, 1999). The social behavioral network is applicable for many mammalian species (Goodson and Kingsbury, 2013). While the basic understanding of the network is based on animal studies, the results are thought to generalize well across mammalian species, including humans, at least to the extent that these regions are involved in the same category of behaviors (Goodson and Kingsbury, 2013; Johnson and Young, 2017; Kelly and Goodson, 2014). In animal models, the types of behaviors related to

this network also appear similar in both sexes (Goodson and Kingsbury, 2013), though the actual behaviors are gender-specific. For example, typical male and female parental roles are not identical, though the social behavioral network does relate to parenting roles in both sexes. The social behavioral network is commonly listed to contain the medial extended amygdala (including the BNST and central medial amygdala), the lateral septum, the medial preoptic area, the anterior hypothalamus, the ventromedial (VMH) and ventrolateral hypothalamus (VLH), paraventricular nucleus of the hypothalamus (PVN), and two midbrain structures, the tegmentum and periaqueductal gray (Goodson and Kingsbury, 2013; Kelly and Goodson, 2014; Newman, 1999); see Fig. 1. Postmortem studies identified two regions of the social behavioral network being altered in MtF transgender individuals: the third interstitial nucleus of the hypothalamus (INAH3), part of the anterior hypothalamus, and the BNST (Garcia-Falgueras and Swaab, 2008; Zhou et al., 1995).

Dimension 3: Incongruence and body-ownership

The involvement of the body-ownership network (Tsakiris, 2010) in gender dysphoria can best be described by first considering how this network is studied in other contexts. The network has often been examined using the rubber hand illusion, whereby an individual is made to feel ownership over a rubber hand by time-locked visual and tactile stimulation to both the observed rubber hand and the unobserved real hand. Time-locked visual and tactile stimulation has also been used to create the illusion of ownership of an entire body that is not one's own. The illusion even persists if the individual shakes hands with what looks like their actual body (Petkova and Ehrsson, 2008). The illusion involves subconscious processing, closely connected with other systems. For example, causing one to feel ownership of a more obese body can cause activation of the distress network, particularly the insula and anterior cingulate cortex (Preston

and Ehrsson, 2016), whereas the illusion of being invisible can reduce subjective and objective social stress measures (Guterstam et al., 2015). Ownership of an artificial limb has also been induced in amputees by replacing the tactile stimulus with electrical stimulation (Collins et al., 2017). The body-ownership network is considered (Grivaz et al., 2017) to include the insula (particularly the left anterior insula), the right ventral premotor cortex, and portions of the posterior parietal cortex (specifically the right and left intraparietal sulci and left superior parietal lobule); see also discussion in Manzouri et al. (2017) and Fig. 1.

The literature based on human data which connects gender dysphoria with the body ownership network and body perception has been continually growing over the last decade. Some early work identified the involvement of the cingulate and insula but failed to associate them with their roles in body perception or distress (Nawata et al., 2010; Zubiaurre-Elorza et al., 2012), having their interpretation instead focused on cerebral dimorphism. The research group of Savic recognized the involvement of body perception networks in gender dysphoria as early as 2011 (Savic and Arver, 2011) and have since published a stream of papers further reinforcing its relevance. Some studies focused purely on anatomical measurements (Burke et al., 2017b; Manzouri et al., 2017; Manzouri and Savic, 2019). Other studies utilized images of the research subject's bodies morphed to look more like the opposite gender (Feusner et al., 2017, 2016). Hormonal treatments were found to reverse the observed anatomical effects and increase consistency between self-perception and actual body image (Burke et al., 2017a; Kilpatrick et al., 2019). The effect of sexual orientation was also found to be a major confounding factor, in that some changes in earlier work thought to be associated with gender dysphoria were found to be explained better by the sexual orientation of the subjects (Burke et al., 2017b; Manzouri and Savic, 2019). However, regions of the body ownership network remained significant even after controlling for sexual orientation (Burke et al., 2017b; Manzouri and Savic, 2019). Note that

homosexual is defined in these studies relative to gender assigned at birth, e.g., an androphylic MtF transgender individual would be labeled as homosexual. One of the regions identified in these studies (Manzouri et al., 2017; Nawata et al., 2010; Zubiaurre-Elorza et al., 2012), the anterior insula, is a common node in both the distress and body-ownership networks, and is interconnected with the central extended amygdala and periaqueductal gray (Kong et al., 2010; Tillman et al., 2018). Beyond the work of Savic, results from a task-based study focused on the body representation network in transgender individuals included changes in the postcentral gyrus and superior parietal lobule (Lin et al., 2014). The authors motivated that study by claiming that the involvement of the body ownership network is a consequence of "dissonance between their biological sex and gender identity". However, all available relevant data are correlational and do not constrain whether changes in body ownership cause, or are caused by, the perception of dissonance.

The body-ownership illusion studies demonstrated that the visual and tactile stimulation must be time-locked to lead to a sense of body-ownership, suggesting that interference in the normal processing of this stimulation could lead to a loss of body ownership. For example, xenomelia is a condition in which individuals feel a given body part is not their own, feel distress, and desire to have it removed. Changes have been observed in the body ownership network using MRI data (Hilti et al., 2012) and cellular activation measured by MEG (McGeoch et al., 2011). Similar changes in MEG activation have been observed in transgender individuals. For example, Case et al. (2017) recorded MEG from female-to-male (FtM) transgender individuals and controls during tactile stimulation to breast and hand. In the FtM transgender individuals, evoked potential response from breast stimulation was reduced relative to hand stimulation, particularly in the intraparietal sulcus (part of the body-ownership network) and primary motor and somatosensory cortecies. Additional electrophysiology results are discussed

by Smith et al. (2015). Thus, sensory perception related to body ownership and both gray and white matter in the body-ownership network (particularly the anterior insula, intraparietal sulcus, and superior parietal lobule) are directly linked with transgender individuals (see asterisks in Fig. 1).

Additional relevant data

We next list additional information about gender dysphoria which should be considered when evaluating hypotheses regarding its cause. Gender dysphoria is a separate construct than just being gender-atypical (American Psychiatric Association, 2013), and gender-atypical individuals do not necessarily experience significant distress nor a decreased ownership of their assigned gender. Additionally, gender dysphoria in younger children has been shown to resolve before puberty without treatment—with some estimates of resolution rate between 55% and 80% (Drummond et al., 2008; Steensma et al., 2011). Common comorbid conditions to gender dysphoria include autism (Strang et al., 2018) as well as other factors typically ascribed to psychosocial factors, specifically anxiety, depression, suicidal ideation and suicide. Treatment for gender dysphoria currently involves gender reassignment, which can include changing one's social presentation and identification as well as bodily alteration via hormonal therapy and/or surgery. Treatments are successful at accomplishing the gender reassignment (see reviews by Hembree et al. (2017) and WPATH (2011)), but outcome measures directly related to distress or body-ownership have not typically been considered nor reported in the past. However, two recent publications did consider perception of body-ownership, but did not specifically consider distress. They found that hormones reverse the anatomical changes in the body-ownership network and increase own-body self-congruent rates (Burke et al., 2017a; Kilpatrick et al., 2019).

The exact cause of gender dysphoria is unknown, but the cause is believed to be biological in nature.

Synthesis of existing data

Previously published data support our hypothesized direct connection between the three specified dimensions of gender dysphoria and the functional roles of the implicated neuronal substrates and networks. Chronic distress is a defining characteristic of gender dysphoria, and multiple nodes of the distress processing network have been found to be altered in transgender individuals using multiple measurement modalities. Behavior atypical of assigned gender is common in individuals with gender dysphoria (with some exceptions depending on age of onset and sexual orientation), and two nodes of the social behavioral network (the network involved in gender typical behavior) have been found to be different in transgender individuals. Lastly, the network for body ownership and self-perception have also been found to be altered, showing changes in both white matter, gray matter, functional connectivity and response to stimuli, including altered sensory response from body parts perceived as incongruous with desired identity. Correlations were also found between affirming hormonal treatment and changes in anatomy of the body ownership network. Thus, the distress, social behavioral, and body-ownership networks each directly match a key dimension of gender dysphoria, and each network has multiple nodes observed to be altered in transgender individuals; see Fig. 1.

Published data do not sufficiently address causality between gender dysphoria and alteration in these three networks. It is possible that the changes in all of these networks are secondary to gender dysphoria, a concept claimed in previous literature for the body-ownership network (Lin et al., 2014). However, the data also allow an alternate interpretation: that changes in these networks are causal to the experience of chronic distress, gender atypical behavior, and

incongruence between perceived gender identity and assigned gender. This view does not minimize the known negative impact of various external factors but instead focuses on developing understanding of what gender dysphoria actually is at a biological level.

The new multisense theory of gender dysphoria

In contrast to existing theories of gender dysphoria, we propose a new theory (the multisense theory) wherein alteration (possibly activational or organizational) in the interacting distress, social behavioral, and body-ownership networks leads to dynamic changes in network activity, causing the subjective experience of gender dysphoria and possible additional, concomitant, observable anatomical changes. While a variety of neuroanatomical changes have been noted (e.g., see reviews by Anand and Altinay (2019), Guillamon et al. (2016), and Smith et al. (2015)), our view specifically addresses the functional significance of the observed changes in the distress network, social behavioral network, and body ownership network, including the neuronal substrates of the BNST, anterior hypothalamus (encompassing the INAH3), anterior insula, intraparietal sulcus, superior parietal lobule, and orbitofrontal cortex. Changes in these substrates support our hypothesis that, in individuals with gender dysphoria, the aspects of chronic distress, gender non-conforming behavior, and incongruence between perception of gender identity and body sex are all directly related to the underlying differences in neurobiology.

We also model that senses based on these networks are integrated with each other and other factors, resulting in an overall sense of gender; see Fig. 2. The underlying neurobiology would influence how much an individual feels chronic distress, how much they desire to act in a manner consistent with their gender role, and how much they feel the gendered aspects of their body belong to them—all of which then contributes to the extent to which an individual feels that

their gender matches that which was assigned at birth, i.e., their overall sense of gender. While the experimental evidence is strongest for the body-ownership/perception network and weakest for the social behavioral network, we allow that the relative weight and causal order of these factors may be different in different individuals. External factors can also influence sense of gender either directly or via affecting the reflexive senses of distress or behavior relative to gender roles. While there is insufficient data to understand the impact of the changes in the precuneus (Manzouri and Savic, 2019), a region which integrates sensory information, a key component of our theory is the integration of multiple senses and factors to form an overall sense of gender.

Discussion

Consistency of the new theory with existing data

Dynamic activity on functional networks. The multisense theory proposes that gender dysphoria is not merely due to static changes in anatomy, as in the previous opposite brain sex theory, but instead includes dynamic activity on interacting, functional networks. This dynamic aspect can explain the distinctness of gender dysphoria from being gender atypical, accounts for the variety of onset ages and both persistent and desistant cases, and is still consistent with the anatomical findings. Changes in sex hormones due to puberty (or aging) could also affect these identified networks, explaining both resolution without treatment in childhood onset causes and the possibility of late-onset cases. Data now support that each of these dimensions (distress, gender conformity, and body ownership/perception) are associated with specific functional neural networks, which is part of the basis of the multisense theory. The multisense theory is also consistent with recent meta-analyses (Altinay and Anand, 2019; Guillamon et al., 2016; Smith et al., 2015): data presented show that brains of transgender individuals are not simply

altered along a male/female dimension to be more like their desired gender, even in studies which controlled for sexual orientation. Thus, overall, available published data are consistent with the multisense theory of gender dysphoria.

Comorbid conditions. The comorbid conditions of anxiety, depression, suicidal ideation and suicide are commonly attributed to having the opposite brain sex as gender assigned at birth as well as psychosocial factors. The latest data challenge that view regarding anatomical brain sex and suggest that altered neuroactivity in the identified networks could also play a key role in these comorbidities. In particular, the distress network, especially the BNST, extended amygdala (Lebow and Chen, 2016) and potentially the insula (Carlson et al., 2011; Tillman et al., 2018), are involved in mood regulation conditions, such as anxiety and depression. Another region altered in individuals with gender dysphoria, the anterior cingulate, is strongly associated with depression (Bunney et al., 2015; Drevets et al., 2008). Recent data also suggest that self-perception, related to the body-ownership network, is altered in individuals with autism (Ropar et al., 2018), another known comorbidity of gender dysphoria. Thus, the underlying mechanisms causing gender dysphoria may also be directly contributing to comorbid conditions, in addition to the indirect contribution mediated by external factors.

Comparison with other theories of gender dysphoria

A prevalent and early theory of gender dysphoria is that it is a manifestation of an actual difference between the person and gendered aspects of their body, assuming that the individual's sense of body ownership and gender identity (their subjective experience) is fully correct (Gooren, 2006). This theory is one basis for sex reassignment as a therapy for gender dysphoria (see, e.g., Fisk (1974)). The initial neuroanatomical studies, which first became available in 1995, also supported this view; see, e.g., Garcia-Falgueras and Swaab (2008) and Zhou et al.

(1995). In these studies, an anatomical difference was found in a sexually dimorphic brain area, with the transgender individual's measurements being closer to that of their desired gender rather than their gender assigned at birth. The associated distress was attributed to the incongruence and/or psychosocial and cultural factors. Gradually it became clear that both structural and functional networks were likely involved (Garcia-Falgueras and Swaab, 2008). However, only recently have data began to be available regarding the biological basis of self-identity and body ownership and its connection with gender dysphoria, e.g., Burke et al., (2017b) and Case et al., (2017).

Another modification was needed when *in vivo* imaging data later demonstrated that brains of transgender individuals also have unique differences relative to cis-gender individuals not fully explained by altered cerebral sexual differentiation, even when controlling for sexual orientation; see papers reviewed by Guillamon et al. (2016) and Smith et al. (2015). One suggestion was that incongruence in limited brain regions is sufficient to cause gender dysphoria (Guillamon et al., 2016). However, anatomical brain sex only appears to be distinctive at the whole brain level, rather than at the level of individual nuclei, within individuals without gender dysphoria (Chekroud et al., 2016; Rosenblatt, 2016). Thus, anatomical incongruence (having a size/shape more like the opposite gender) in limited regions is typical in individuals without gender dysphoria and is not likely to be sufficient to cause gender dysphoria.

The multisense theory, however, does not preclude that some anatomical changes associated with gender dysphoria may appear as atypical cerebral sexual dimorphism nor does it preclude involvement of sex hormones; the multisense theory interprets these changes based on the functional implications. For example, the functional significance of alteration in the BNST (Zhou et al., 1995) was not understood until long after 1995 and thus these results were originally interpreted relative to sexual dimorphism. Similarly, the functional significance of

some other alterations are not yet fully understood. If such alterations are fundamental to gender dysphoria and not just secondary effects, then the prediction of the multisense theory is that the functional significance will relate to the distress, body-ownership, and/or social behavioral network, with the level of sexual dimorphism being less relevant.

Another modification to the opposite brain sex theory was recently proposed by Altinay and Anand (2019). In this theory, sense of gender does not arise from limited cerebral sexual dimorphism, but rather from "brain gender," which they defined as "gender identity specific brain architecture and organization." While Altinay and Anand suggest brain gender might be the body ownership network, they do not clearly define what brain gender actual means in terms of neurobiology, and instead focus on interactions with external stimuli and how this would feed into distress via cognitive dissonance. The multisense theory also recognizes the influence of external stimuli (see Fig. 2), including how cognitive dissonance could increase distress. However, the multisense theory does not encapsulate all anatomical changes into a "brain gender" nor place distress as only secondary to other changes. Instead, the multisense theory details how changes in specific networks relate to specific reflexive senses (which would impact the overall sense of gender) and allows for the possibility that several of these networks could be causal to the condition in some individuals.

One other theory of gender dysphoria has also been proposed which does not directly involve alterations in cerebral sexual differentiation. Manzouri and Savic (2019) "suggest that [gender dysphoria] is... specifically linked to cerebral networks mediating self-body perception" rather than a "less pronounced cerebral sex dimorphism," an idea expressed in multiple papers from their group. The multisense theory includes this concept as one component but also extends beyond this idea to explain other symptoms of gender dysphoria by incorporating other important networks.

One might argue that the general success of gender identity affirmation treatments for gender dysphoria supports only theories based on a brain/body sex incongruence. However, the argument depends on the mechanisms of how treatments affect symptoms, which is currently unknown. Both males and female brains need estrogen and testosterone. Changes in these hormones could potentially affect the body-ownership, social behavioral, and/or distress networks. For example, the impact of affirming hormone treatment (testosterone for FtM individuals, estrogens and anti-androgens for MtF individuals) was recently studied for individuals with gender dysphoria. In both FtM and MtF individuals, hormone treatment increased own-body self congruence rates (even though no surgical alterations were yet performed) and it also resulted in cortical thickness returning to be more like that of individuals without gender dysphoria (Kilpatrick, et al., 2019). The exact mechanism is unknown, but both hormone treatments would increase estrogen in the brain, either directly (MtF) or indirectly via aromatization (FtM). Thus, the partial efficacy of current treatments may be due, in part, to the hormones indirectly influencing the body ownership, distress and/or social behavioral networks. Additionally, external factors such as diagnosis with gender dysphoria or receipt of a treatment plan could also impact sense of gender and symptoms of gender dysphoria, including potentially increasing or decreasing distress. Given that the mechanism leading to the efficacy of current treatments is not yet well understood, efficacy of current treatment thus does not exclude the multisense theory of gender dysphoria and provides little disambiguation between theories of gender dysphoria.

Interaction with other networks

Sexual and romantic partner preference. Subtypes of gender dysphoria have been proposed based on sexual orientation and onset age (Blanchard, 1989), though the subtype labels

do not necessarily match the subjective experience of individuals with gender dysphoria (Gooren, 2006). Another recent paper concluded that MtF individuals with early and late onset gender dysphoria have statistically significant differences in their sexual orientation, though the data show a variety of sexual orientations being present in both subtypes (early onset cases being only 52.6% percent attracted to men) (Zavlin et al., 2019). The multisense theory allows for two possible explanations for correlation between gender dysphoria, onset age, and partner preference, detailed in the next two paragraphs. These two possibilities are not mutually exclusive.

The first explanation is that gender dysphoria and partner preference represent different underlying mechanisms, but interaction between the mechanisms causes appearance of subtypes. While gender dysphoria appears related to internally focused senses (sense of own gender, described earlier), partner preference appears related to externally focused senses, particularly sense of the gender of others. For example, a recent MRI study suggested that homosexuality may involve altered interpretation of external sensory stimuli (Manzouri and Savic, 2018), consistent with earlier work from their group regarding processing of smell and partner preference (Berglund et al., 2006; Savic et al., 2005). Given available data, detailed below, we hypothesize that partner preference is connected with the neurohormone vasopressin in brain regions related to social recognition (specifically the lateral septum), affecting the subconscious, sensory response to the gender of others. In some cases, this change could result in equivalent subconscious response to all genders (bisexual partner preference). In other cases, this change, combined with other factors, could cause the perception that the opposite gender is too different to be a sufficiently compatible partner (homosexual partner preference). Human data supporting this hypothesis include Swaab and Hofman (1990), which found that the number of vasopressin secreting neurons in the SCN of male homosexuals averaged three times larger than male and

female heterosexual controls. At the time, interpretation focused on the overall shape (homosexual males having an overall shape more like females than males), rather than the number of vasopressin secreting cells in homosexual men being distinct from both male and female heterosexual individuals. In animals, increases in the number of vasopressin secreting neurons and bi- and homosexual behavior were also observed in male rats treated with an aromatase inhibitor during the perinatal SCN developmental period (Bakker et al., 1993; Swaab et al., 1995). Aromatase enzyme knock-out (ArKO) male mice exhibited decreased social recognition (vocalizing towards both genders instead of just females), decreased habituation to test female mice, and decreased vasopressin in the lateral septum (a node in the social behavioral network); the behavior and vasopressin levels in the lateral septum were restored to control levels with adulthood administration of dihydrotestosterone (DHT) and estrogen (Pierman et al., 2008). Other rat studies also support vasopressin in the lateral septum having a role in social recognition (Bychowski et al., 2013). Human studies corroborate these findings, with data supporting the role of vasopressin in bonding (Atzil et al., 2012), cooperative risk (Brunnlieb et al., 2016), and other aspects of social recognition and behavior (see review by Johnson and Young (2017)). In humans, it is possible that an increased number of vasopressin secreting cells in the SCN, as found in homosexual men, could lead to too low of vasopressin in the lateral septum due to compensatory effects. Changes in septal areas have actually been associated with partner preference in humans (Poeppl et al., 2016). Thus, while more research is needed in humans (especially females) in order to develop a complete model of partner preference and its relationship to gender dysphoria, the data suggest the plausibility of our hypothesis regarding partner preference, vasopressin, and the lateral septum. Interaction between these closely connected regions could thus explain the subtypes, though stronger data is needed before

including these factors in our multisense model of gender dysphoria. Evidence does suggest that partner preference, like gender dysphoria, also involves sensory perception.

The second explanation for the correlation between gender dysphoria, onset age, and partner preference centers on relative timing. Assume that partner preference is encoded in the brain in the relative terms of "same" and "different" (as sense of gender is encoded in the brain in the multisense theory) rather than absolute "male" and "female." Then an individual attracted to opposite gender could be attracted to either males or females depending on what they sensed their gender to be when they developed partner preference; likewise, individuals attracted to the same gender could also be attracted to either males or females. Late onset cases are likely to occur after development of partner preference. Thus the subtypes emerge: individuals with early onset gender dysphoria would tend to be labeled by Blanchard as homosexual subtype, and most individuals with late onset gender dysphoria would be labeled by Blanchard as non-homosexual subtype. It is not yet clear why the subtypes appear stronger in males than females. However, the defining characteristic of the subtypes appears to be the onset age of gender dysphoria, not the sexual orientation.

Sleep/wake and circadian. Each of the three identified networks have significant overlap and anatomical connections with the sleep/wake and circadian timing systems. This includes the VMH (social behavioral network) (Orozco-Solis et al., 2016; Orozco-Solis et al., 2015), the BNST (distress and the social behavioral network) and lateral septum (social behavioral network) (Saper et al., 2005b), and the insula (distress and body ownership networks) (Chen et al., 2016). Circadian dysregulation may also be involved in the association between gender dysphoria and its comorbidities. For example, circadian dysregulation in the anterior cingulate, a region found to be different in individuals with gender dysphoria, is associated with depression (Bunney et al., 2015). Genetic studies also provide weak support for a connection

between gender dysphoria and sleep/circadian, though the data are not overly specific. While results from large-scale, genetic association studies are not yet available, the candidate genes identified in small cohort studies are all associated with sex hormones (Cortes-Cortes et al., 2017; Fernandez et al., 2014a, 2014b; Hare et al., 2009; Henningsson et al., 2005; Ujike et al., 2009) or the ryanodine type-3 receptor (Yang et al., 2017), all of which influence the sleep/wake and circadian system (Vasalou and Henson, 2010; Whitt et al., 2018). Thus, in general, the available data support possible relationships between sleep/circadian and gender dysphoria, though the data are not definitive and do not quantify the relative importance of sleep/circadian factors. We do note that one case study makes an unsupported statement that sleep disorders are higher in children with gender dysphoria (Kern et al., 2014), though direct empirical evidence does not seem to be available. Thus, future studies are merited to understand how sleep/circadian influences gender dysphoria and its comorbidities, how treatments for gender dysphoria influence sleep via sex hormone changes, and the extent to which sleep disorders are comorbidities of gender dysphoria.

Future directions

The multisense theory of gender dysphoria suggests future research studies that could improve understanding of gender dysphoria and provide data to further test/validate related theories. One direction of future research would be to continue to disentangle the association of neural substrates and networks with each of the three noted dimensions of gender dysphoria. Additional controls are needed, such as individuals with gender atypical behavior during childhood or other ages without gender dysphoria but of each sexual orientation, and individuals with other chronic distress or body-ownership conditions, such as body dysmorphic disorder, xenomelia, anorexia, and depersonalization. This will allow further stratification of the

relationship between behavioral effects and specific neural networks. Additionally, it will be essential to assess individuals with gender dysphoria rather than the larger population of transgender individuals, an important distinction present in some recent work (e.g., Feusner et al. (2017)). Not all transgender individuals necessarily have gender dysphoria.

Future studies should also address how treatment affects specific dimensions of gender dysphoria, which is quite limited in current data. Treatment outcome measures have often been designed to assess satisfaction with new gender and effectiveness of the gender reassignment (e.g., see discussions in Hembree et al., (2017) and WPATH (2011)). These measures do not adequately assess the dimension of distress, the effect on body ownership, or the impact of hormonal treatments on sleep and circadian function. For example, recent data suggest that hormone treatment alone may directly address some of the underlying neurobiology and reduce the incongruence of own-body perception (Kilpatrick et al., 2019). We additionally recommend that future research regarding treatment outcomes specifically and directly assess distress and body-ownership in their primary outcomes, as well as effects upon sleep/wake and circadian phase in their secondary outcomes.

The multisense theory can also help facilitate future research separating out predisposing, precipitating, and perpetuating factors of gender dysphoria. For example, an increase of distress, due to internal or external factors could potentially cause an atypical child with a predisposition for gender dysphoria to develop the condition, or alternately cause an individual to have persistent gender dysphoria when it otherwise would have resolved. Extending the framework of the multisense theory to include predisposing, precipitating, and perpetuating factors will allow progress towards understanding causal relations (including interactions and feedback) between changes in the identified networks, external factors, and the related dimensions of gender dysphoria.

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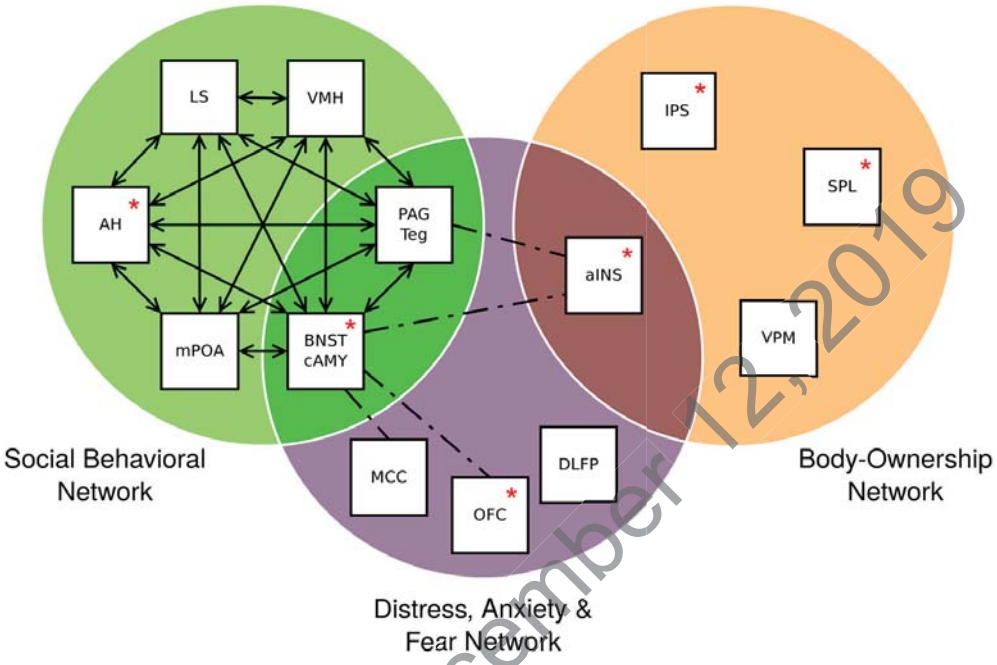
570 **Figures and captions**



571 **Figure 1. Networks related to key dimensions of gender dysphoria.** Each box represents
572 nuclei or brain regions involved in these networks. Red asterisks are included in boxes where
573 the regions/nuclei have known anatomical changes associated with transgender individuals
574 (Altinay and Anand, 2019; Guillamon et al., 2016; Smith et al., 2015): anterior hypothalamus
575 (AH) (Garcia-Falgueras and Swaab, 2008), BNST (Zhou et al., 1995), anterior insula (aINS) and
576 orbitofrontal cortex (OFC) (Zubiaurre-Elorza et al., 2012), superior parietal lobe (Lin et al.,
577 2014), and intraparietal sulcus (IPS) (Case et al., 2017). Connections based on Kong et al.,
578 (2010), Newman (1999), and Tillman et al. (2012). Abbreviations: AH, anterior hypothalamus;
579 aINS, anterior insula; BNST, bed nucleus of the stria terminals; cAMY, central amygdala; DLPF,
580 dorsolateral prefrontal cortex; IPS, intraparietal sulcus; LS, lateral septum; MCC, mid-cingulate
581 cortex; mPOA, medial preoptic area; OFC, orbitofrontal cortex; PAG, periaqueductal gray; SPL,

582 superior parietal lobe; Teg, tegmentum; VMH, ventromedial hypothalamus; VPM, ventral

583 premotor cortex.

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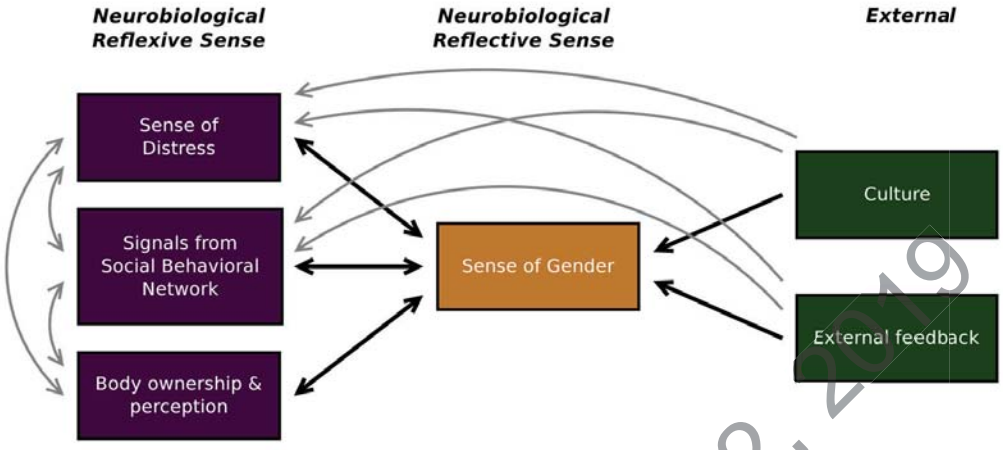

Figure 2. Diagram of the multisense theory of gender dysphoria. One's overall sense of gender is modeled as a neurobiological, reflective sense, integrating information from multiple senses and stimuli (bold arrows). This sense of gender is framed relative to gender assigned at birth (e.g., am I the gender which was assigned at birth?) rather than an absolute male/female dichotomy (e.g., am I female?). Each of the three listed reflexive senses (purple boxes) relate to a specific dimension of diagnostic criteria for gender dysphoria as well as a matching functional network with nodes known to be altered in transgender individuals (Fig 1). The interaction between sense of gender and these three reflexive senses may be bidirectional. External factors (green boxes) influence sense of gender either directly (bold arrow) or indirectly via affecting the reflexive senses. The model can also be extended to include additional internal and external factors. The diagram represents a dynamic network, not a specific causal pathway, and includes potentially complex interactions and feedback loops.