Review article

Meltem Kiyar, Sarah Collet, Guy T'Sjoen and Sven C. Mueller*

Neuroscience in transgender people: an update

https://doi.org/10.1515/nf-2020-0007

Abstract: Transgender persons identify with a gender different from the one they were assigned at birth. Although describing oneself as transgender is not a new phenomenon, media attention has lately been increasing exponentially, thanks to progressive changes in laws and change in societal attitudes. These changes also allow more people nowadays to (openly) identify as transgender and/or seek gender-affirming treatment. However, simultaneously, not much is presently understood about the underlying neurobiology, and specifically the brain structure and brain function of transgender persons. One major question in neuroimaging and neuroscience has been to determine whether, at the brain level, transgender people resemble more their gender identity, their sex assigned at birth, or have a unique neural profile. Although the evidence is presently inconsistent, it suggests that while the brain structure, at least before hormonal treatment, is more similar to sex assigned at birth, it may shift with hormonal treatment. By contrast, on "sex-stereotypical tasks," brain function may already be more similar to gender identity in transgender persons, also before receiving gender-affirming hormone treatment. However, studies continue to be limited by small sample sizes and new initiatives are needed to further elucidate the neurobiology of a 'brain gender' (sex-dimorphic change according to one's gender).

Keywords: cross-sex hormones; gender; magnetic resonance imaging; neurobiology; trans

Meltem Kiyar and Sarah Collet contributed equally and share first authorship.

***Corresponding author: Sven C. Mueller**, Department of Experimental Clinical and Health Psychology, Ghent University, Henri Dunantlaan 2, 9000, Ghent, Belgium, E-mail: sven.mueller@ugent.be
Meltem Kiyar: Department of Experimental Clinical and Health Psychology, Ghent University, Ghent, Belgium
Sarah Collet and Guy T'Sjoen: Department of Endocrinology and Center for Sexology and Gender, Ghent University Hospital, Ghent, Belgium

Zusammenfassung: Transgender-Personen identifizieren sich mit einem anderen Geschlecht als dem bei der Geburt zugewiesenen. Obwohl Menschen, die sich mit einem anderen Geschlecht identifizieren, kein neues Phänomen sind, so ist die mediale Aufmerksamkeit in den letzten Jahren diesbezüglich exponentiell gestiegen. Dies ist auch den gesetzlichen Verbesserungen und einer Veränderung in der gesellschaftlichen Einstellung zu dem Thema zu verdanken. Zur gleichen Zeit aber wei man noch nicht viel über die Gehirnstruktur und Gehirnfunktion bei transgender Menschen. Eine Hauptfrage in den Neurowissenschaften ist es, ob die Gehirne von Transgender-Personen jenen ähneln des Geschlechtes, dem sie bei der Geburt zugewiesen wurden, des Geschlechtes mit dem sie sich identifizieren, oder ob sie ein unabhängiges neuronales Profil aufzeigen. Obwohl die Befunde derzeit widersprüchlich sind, zeigen sie in die Richtung, dass sich die Gehirnstruktur vor der hormonellen Behandlung nur unwesentlich verändert. Auf der anderen Seite gleicht die neuronale Aktivität bei "geschlechtstypischen Aufgaben" von Transgender-Personen der neuronalen Aktivität ihres identifizierten Geschlechts (auch schon vor der Hormonbehandlung). Trotzdem sind Studien weiterhin limitiert, da sie oft mit kleinen Stichproben auskommen müssen und neue Initiativen zur Bestätigung der ersten Befunde nötig sind.

Schlüsselwörter: Sexualhormone; Gender; Magnetresonanztomographie; Neurobiologie; trans

Introduction

An increasing interest in, and attention to, the life and experiences of transgender persons can be seen in a surge in movies, books, television shows, newspaper reports, and academic articles. *Transgender* persons experience an incongruence between the sex they were born with and their gender identity, which can be described as our internal experience and naming of gender. Some individuals are born as female, but identify as male, hereafter *transgender men*. Other individuals are born as male and identify as female, hereafter *transgender women*. The term "transgender" is broad and should be considered as an umbrella term for people whose gender identity differs from the sex they were born with. It includes a whole spectrum of genders: not only does it comprise people whose gender identity is the opposite of their sex at birth, it also characterizes people who are not exclusively masculine or feminine. This phenomenon is referred to as being *gender nonbinary* or *genderfluid*. In addition, some individuals can also identify themselves as *gender-nonconforming*. It is important to note that being transgender is independent of sexual orientation. Readers specifically interested in gender nonbinary or genderfluid persons are referred to the review of Richards et al. (2016). Contrary, *cisgender people* do not experience gender incongruence, implying that their gender identity or expression matches the sex they were born with. Although transgender does not exclusively include transgender men and women as mentioned before, we will focus in this paper on these two groups for the sake of clarity, knowing categorizing people always implies inaccuracies.

Clinical management of gender dysphoria and transgender persons

Recent population studies estimate prevalence rates at 4.6 transgender persons per 100,000 individuals (Arcelus et al., 2015). Some, but not all, transgender persons experience gender dysphoria, defined as the discomfort or distress that is caused by this discrepancy between gender identity and the sex they were born with (and the associated gender role and/or primary and secondary sex characteristics). Classification systems such as the International Classification of Diseases (ICD) and the Diagnostic Statistical Manual of Mental Disorders (DSM) are used to diagnose gender dysphoria. In ICD, see under "Conditions related to sexual health"; in DSM, see under "Gender dysphoria." Gender dysphoria may result in negative effects on one's psychological, physical, and social well-being. Psychological counseling and *gender-affirming medical treatment* are often wished for by a large proportion of transgender persons. Diagnosis and treatment of individuals suffering from gender dysphoria require a multidisciplinary approach, which might involve psychologists, endocrinologists, psychiatrists, urologists, gynecologists, dermatologists, surgeons, but also voice and communication therapists (i. e., to adapt their voice and manner of speaking to their identified gender, for example). Furthermore, treatment depends on individual needs: some persons only verbalize a wish for psychological support and guidance in the coming-out process, while others may require psychotherapeutic interventions to treat frequently occuring mental health problems such as mood and anxiety disorders (Branstrom and Pachankis, 2020; Heylens et al., 2014). Others may need gender-affirming hormone therapy (GAHT) and/or surgery to increase the match between their gender identity and expression. Guidelines for treatment are described by the World Professional Association for Transgender Health and the Endocrine Society. GAHT has been shown to effectively alleviate gender dysphoria and reduce anxiety, depression and suicide attempts of transgender persons (e. g., Branstrom and Pachankis, 2020).

The process of gender-affirming treatment is different for transgender women and transgender men. Transgender women's physical transition starts with high testosterone levels (i. e., the primary male sex hormone), and they need female sex hormones, i. e., estrogen in order to obtain feminization (breast development, fat and muscle distribution). Transgender men will need testosterone for masculinization of their physical appearance (voice deepening, masculine pattern of hair, fat and muscle distribution) as they start with testosterone levels in the female range.

Brief historical overview of transgender persons

Historically, although awareness for, and development of, the transgender community only started in the second half of the 20th century, the history of transgender identities goes back to various cases recorded in multiple ancient civilizations. In numerous cultures, multigender roles were recognized and documented with women who passed as men and vice versa by adopting clothes and roles of respective genders. The Chevalier d'Éon de Beaumont, a spy in the French king's service, is one of many examples. It was considered that d'Éon may have been a transgender woman, as he successfully infiltrated Russian court identifying as a female (Burrows, 2011). The first known European transgender person to undergo gender-affirming surgery was Dora Richter. She underwent genital surgery, first removing the testicles (i. e., orchiectomy) in 1922, followed by the removal of the penis and a vaginoplasty in 1931 in Berlin, Germany (Mancini, 2010). Lili Elbe (portrayed in the factually inaccurate movie *The Danish Girl*) underwent gender-affirming surgery in Germany in the 1930s. The surgeries of both transgender women were, at that time, highly experimental. with a high risk for adverse effects. Following infection-related complications, Lili Elbe died 3 months after surgery, whereas the fate of Dora Richter is unknown (Providentia, 2010). About 20 years later, Christine Jorgensen, an American transgender woman, went to Denmark for gender-affirming surgery, a story that was covered by a *New York Daily News* front-page story (Bullough, 2009; Khan, 2016). Even though female sex hormones (i. e., estrogens) were first chemically synthesized in the 1920s and 1930s (Watkins, 2007b), the European pioneers probably did not use these, as the development of sex hormones started in the United States (Watkins, 2007a). The first professional association for gender dysphoria, now known as the World Professional Association for Transgender Health, was formed in 1979.

Neurobiology of transgender research

Surprisingly, relatively little is known regarding the underlying neurobiology of a transgender identity. Within the field of neuroscience, a landmark study in 1995 documented that part of the forebrain circuit (i. e., the bed nucleus of the stria terminalis [BNST] in transgender women was found to be similar in size as in cisgender women (Zhou et al., 1995). Moreover, differences in volume in the BNST have been found for cisgender men and women (Zhou et al., 1995). More specifically, the BNST was found to be larger in men relative to women showing a sexdimorphic pattern (Zhou et al., 1995). To measure this, post mortem brains were used. However, because the transgender women had received GAHT (i. e., estrogens), it was difficult to determine the impact that hormonal treatment may have had on the findings. Since the advent of the first *in vivo* magnetic resonance imaging (MRI) performed on humans (Belliveau et al., 1991), scientists nowadays are keen to examine the extent to which the brains of transgender persons show different brain *structural* properties (gray and white matter, cortical thickness, volume, and surface area) as well as brain *functionality* (functional MRI [fMRI]) and *connectivity* between brain areas (diffusion tensor imaging [DTI], functional and structural connectivity) (Figure 1). Although brain imaging studies have consistently documented brain differences between cisgender males and cisgender females, this has not been the case for transgender persons. Thus far, no clear explanation or neurobiological underpinning of being transgender has been identified (Mueller et al., 2017). Nonetheless, some progress has been made. Most neurobiological studies aim to investigate whether the brain of transgender persons resembles that of the sex they were born with, that of their gender identity, or a specific intermediate brain type. In terms of structural properties, total brain volume and the gray matter volume in the brains of

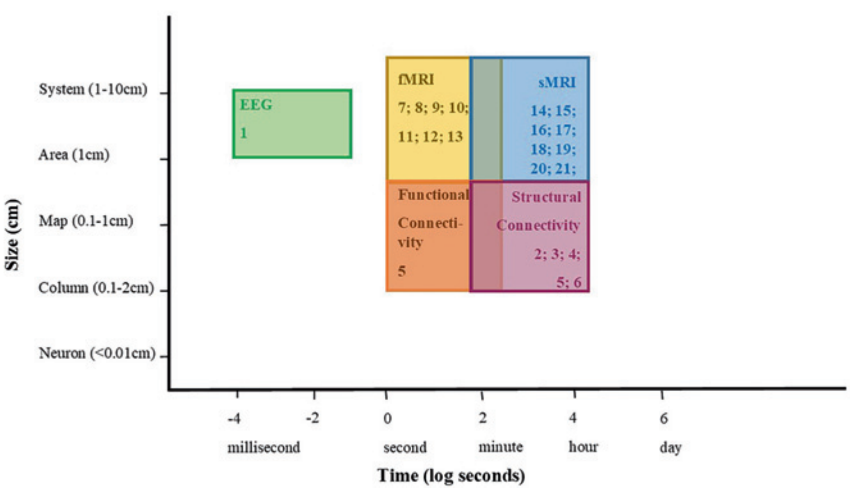

Figure 1: Graphical summary of some of the currently available neuroimaging techniques used in transgender research presented in the current review. This figure illustrates the sites of action in the brain on the vertical axis, indicating the smallest and largest sizes of the region from which the technique provides information. The horizontal axis represents the temporal dimensions over which information can be collected with each technique. The spatio-temporal capabilities are depicted by colored rectangles per neuroimaging technique. Reviewed papers are categorized per technique. Figure loosely modeled after Churchland and Sejnowski (1988). NB. sMRI and fMRI are acquired similarly; however, anatomical brain structure varies less in function of time compared to neuronal brain function. Electroencephalogram (EEG): (1) Künzel et al. (2010). Functional and structural connectivity: (2) Kranz et al. (2014); (3) Rametti et al. (2011a); (4) Rametti et al. (2011b); (5) Manzouri and Savic (2018); (6) Hahn et al. (2015). Functional MRI (fMRI): (7) Berglund et al. (2008); (8) Burke et al. (2014); (9) Carrillo et al. (2010); (10) Schöning et al. (2010); (11) Soleman et al. (2013); (12) Sommer et al. (2008); (13) Burke et al. (2016). Structural MRI (sMRI): (14) Zhou et al. (1995); (15) Savic and Arver (2011); (16) Luders et al. (2009); (17) Luders et al. (2012); (18) Zubiaurre-Elorza et al. (2013); (19) Hulshoff Pol et al. (2006); (20) Kim et al. (2015); (21) Zubiaurre-Elorza et al. (2014); (22) Seiger et al. (2016).

transgender persons who did not yet receive GAHT were similar relative to their sex assigned at birth (Savic and Arver, 2011). Although some studies show reduced gray matter volume in transgender women without GAHT relative to both cisgender groups (Luders et al., 2009), cortical thickness is increased in transgender women when compared to cisgender men, including both hemispheres, as well as the orbitofrontal cortex, and the insular and medial occipital cortices (Luders et al., 2012; Zubiaurre-Elorza et al., 2013). Furthermore, frontal and parietal cortical thickness was also larger in transgender men and cisgender women compared to cisgender men (Zubiaurre-Elorza et al., 2013).

Advances in software and computer technology have enabled to assess the intrinsic connections between brain regions. Connectivity refers to structural and functional links between different brain areas. Whereas structural connectivity describes how the white matter tracts physically connect distinct brain areas, functional connectivity represents the relationship between brain regions in how their neural activity varies (i. e., oscillates) across time together. Studies have revealed an intermediate white matter microstructure in transgender men and women relative to that of cisgender men and women. For example, the white matter tracts between the frontal lobe and the parietal lobe are less strongly connected in transgender persons relative to cisgender persons (Manzouri and Savic, 2018). Furthermore, trans people have been found to differ in their axonal organization of the white matter (Rametti et al., 2011a, b) and their rate of diffusion of molecules and water in the brain (Kranz et al., 2014) taking in-between positions between cisgender men and women. Another study showed a decreased structural connectivity between the left and right hemispheres in transgender relative to cisgender persons (Hahn et al., 2015). Presently, two hypotheses have been put forward why certain brain areas would evidence structural differences between transgender and cisgender persons. Although one theory focuses on neural developmental patterns and contributions of hormones and hormone receptors to brain development (Guillamon et al., 2016), the other theory centers around brain areas in which there is a discrepancy between the notion of one's gender identity and one's brain representation of one's body (Feusner et al., 2017). As of yet, it is too early to determine which theory might find more support, also in light of recent evidence suggesting compatibility between the two hypotheses (Uribe et al., 2020).

In comparison to studies on brain structure, research on brain activity in transgender persons is lagging behind. Several reasons may be responsible for this including: 1) the need to first establish anatomical differences before functionality can be addressed, 2) the relatively small number of laboratories doing neuroimaging research in this cohort, and 3) the need for highly interdisciplinary research teams requiring presence of teams with experience in functional MRI. Existing work has predominantly focused on tasks eliciting "sex-typical" brain responses and determining, similar to structural imaging work, whether the brain activity of transgender persons resembles those of their sex assigned at birth or their gender identity. As such, studies have focused on olfactory processing (Berglund et al., 2008; Burke et al., 2014), mental rotation (Carrillo et al., 2010; Schöningen et al., 2010), or verbal fluency (Soleman et al., 2013). Olfactory processing could be described as a primitive function that is essential to survival and procreation. Males and females are sensitive to steroid compounds acting as pheromones. These chemicals, which signal, among others, alarm, food, or sexual attraction, can influence the behavior of the receiving individual. As a consequence, it can lead to the activation of the hypothalamus. Surprisingly, transgender women's brains (hypothalamus) responded similar to cisgender women's brains when encountering a male pheromone (Berglund et al., 2008). However, sexual development appeared to play a role as this biological shift toward the identified gender appeared during the onset of puberty, when hormonal levels rise (Burke et al., 2014). Before the start of puberty, transgender youth resembled the sex assigned at birth on this olfactory task (Burke et al., 2014). Other, more abstract cognitive functions are also known to dissociate between males and females, i. e., being sex-stereotypical. For example, men tend to be, on average, slightly better than women to mentally rotate objects in space. Here, transgender women resembled their identified gender as they showed reduced brain activity in the parietal lobe, a brain region crucial for this skill, while mentally manipulating 2D and 3D objects in space (Carrillo et al., 2010). This was confirmed by Schöningen et al. (2010), who documented an increased parietal cortex activation in cisgender men relative to transgender women (with and without GAHT) during such a mental rotation task. Conversely, women tend to be better, on average, than men, when retrieving verbal information from memory (i. e., verbal fluency). During the verbal fluency task, transgender girls showed relatively better performance (i. e., retrieved more words) than cisgender boys, cisgender girls and transgender boys (Soleman et al., 2013). However, the participants' brain activation did not resemble either the gender identity or sex assigned at birth but had a unique neural profile (Soleman et al., 2013).

Even more scarce are studies that examine the effects of long-term GAHT on the brain. Limited data suggest that some structures of the brain develop toward the direction of the gender identity in transgender persons with hormonal treatment (Hulshoff Pol et al., 2006; Kim et al., 2015; for a review, see Smith et al., 2015). Although the hypothalamus in transgender women decreases in size after GAHT (Hulshoff Pol et al., 2006), it increases in size in transgender men (Kim et al., 2015). Additionally, proportionately, transgender women's brains decreased in size with GAHT, while transgender men's brains increased in total brain volume (Hulshoff Pol et al., 2006). This was not only true for overall volume but also cortical thickness, which increased after 6 months of hormonal treatment in transgender men, and decreased in transgender women (Zubiaurre-Elorza et al., 2014; Seiger et al., 2016). In a very small sample (transgender men, $n = 6$; transgender women, $n = 8$), Sommer et al. (2008) documented increases in brain activity after GAHT in a language task but not a mental rotation task. Yet, neural activation to the language task was related to post-treatment estradiol levels, while neural activation to mental rotation was related to post-treatment testosterone levels for both sexes (Sommer et al., 2008). Adding to these findings is a study in adolescents, in which brain activation during mental rotation increased with testosterone treatment in transgender girls (Burke et al., 2016). Even though studies aiming to confirm these initial findings are slowly increasing, more research is necessary.

Future directions

Although the number of transgender persons presenting to the gender clinics has increased, the understanding of the neurobiology is only slowly catching up. Whereas studies on structural brain properties are becoming available, work using functional MRI remains scarce. A continuing challenge will be the relatively small numbers in MRI studies (sample sizes are often limited to 10–25 individuals per group) (Schöning et al., 2010; Sommer et al., 2008), lack of cisgender control groups for comparisons (Kim et al., 2015), absence of pretreatment data (Carrillo et al., 2010), lack of taking into consideration confounding factors (e. g., age of onset of gender dysphoria, sexual orientation, non-sex-specific hormonal affects affecting both sexes), or the absence of studies on gender nonbinary persons. In addition, country- and culture-specific phenomena (for example, availability of type of GAHT, legal structures, through which transgender persons are recruited) might also affect study strategies and therefore their findings. As such, increasing the amount of studies, taking into account neuroimaging together with GAHT, is essential for future research. A first step in this direction is the ENIGMA Transgender Persons Working Group, which aims to share and pool neuroimaging data across countries and professionals to increase the study sample size (http://enigma.ini.usc.edu/ongoing/enigma-transgender-persons/). In addition, parallel neurobiological research has slowly begun to elucidate epigenetic influences on the brain (Cortes et al., 2019) as well as charting the genetic variation, presently mostly those involved in hormonal regulation (Fernandez et al., 2018), in transgender persons. Finally, translational animal work has begun to examine the influence of hormones on brain metabolites using a female rat model of androgenization (Perez-Laso et al., 2018). Thus, future synthesizing work will be able to inspect all of these lines of research to draw a neurobiological picture of a “brain

Conclusions

This review sought to provide a brief overview on the current knowledge in neuroimaging studies in transgender persons. Much progress has been made over the past 25 years trying to detect the neurobiological underpinnings of gender dysphoria and identifying the existence of a brain gender. Nonetheless, many findings remain inconsistent. As such, increased collaboration strategies are essential for further research validation.

Funding: This work was supported by an interdisciplinary research project from the special research fund (BOF) granted to S.C.M. and G.T (IOP003–18).

Glossary

Cisgender person: A person whose gender identity is congruent with his or her sex assigned at birth, for example, a person assigned female at birth with a female gender identity.

Gender-affirming medical treatment: An inclusive term for a number of gender-affirming medical interventions including gender-affirming hormone therapy and gender-affirming surgery.

Gender-affirming hormone therapy (GAHT): The primary medical intervention sought by transgender persons inducing the acquisition of secondary sex characteristics more aligned with the experienced gender identity. For example, a transgender man will receive testosterone treatment, whereas a transgender woman will receive estrogens and testosterone blockers.

Gender-affirming surgery: A range of surgical interventions available to transgender persons who wish to alter physical appearance or function to reduce gender incongruence.

Gender nonconformity: An individual who does not conform to a given gender role in a particular culture.

Gray matter: Contains the neuronal cell bodies and unmyelinated axons, which play a key role in controlling sensory and muscular activity.

In vivo: In a living organism.

Orchiectomy: A surgical procedure in which one or both testicles are removed.

Phalloplasty: A surgical (re)construction of the penis.

Pheromone: A chemical substance that serves as a stimulus for eliciting behavioral responses.

Post mortem: Occurring after death.

Transgender: An umbrella term to describe individuals whose gender identity varies from their sex assigned at birth.

Transgender man: A person whose sex was assigned female at birth, but identifies as male.

Transgender woman: A person whose sex was assigned male at birth, but identifies as female.

Steroids: Biologically active compounds functioning as signaling molecules.

Vaginoplasty: A surgical (re)construction of the vagina.

Verbal fluency: Cognitive function facilitating retrieval of information from memory. This can be measured by a psychological test in which participants have to produce as many words as possible from a category in a given time. For example, finding words beginning with the letter L.

References

Arcelus, J., Bouman, W.P., Van Den Noortgate, W., Claes, L., Witcomb, G., and Fernandez-Aranda, F. (2015). Systematic review and meta-analysis of prevalence studies in transsexualism. Eur. Psychiatry *30*, 807–815.

Belliveau, J.W., Kennedy, D.N., Jr., McKinstry, R.C., Buchbinder, B.R., Weisskoff, R.M., Cohen, M.S., Vevea, J.M., Brady, T.J., and Rosen, B.R. (1991). Functional mapping of the human visual cortex by magnetic resonance imaging. Science *254*, 716–719.

Berglund, H., Lindström, P., Dhejne-Helmy, C., and Savic, I. (2008). Male-to-female transsexuals show sex-atypical hypothalamus activation when smelling odorous steroids. Cereb. Cortex *18*, 1900–1908.

Branstrom, R., Pachankis, J.E., 2020. Reduction in mental health treatment utilization among transgender individuals after gender-affirming surgeries: A total population study. Am. J. Psychiatry. https://doi.org/10.1176/appi.ajp.2019.19010080.

Bullough, V.L. (2009). Jorgensen, Christine (30 May 1926–3 May 1989), who achieved fame by undergoing a surgical sex change. [online] https://web.archive.org/web/20090222002724/http://www.libarts.ucok.edu/history/faculty/roberson/course/1493/supplements/chp27/27.%20Christine%20Jorgensen.htm.

Burke, S.M., Cohen-Kettenis, P.T., Veltman, D.J., Klink, D.T., and Bakker, J. (2014). Hypothalamic response in gender dysphoric children and adolescents. Endocrinology *5*, 1–10.

Burke, S.M., Kreukels, B.P., Cohen-Kettenis, P.T., Veltman, D.J., Klink, D.T., and Bakker, J. (2016). Male-typical visuospatial functioning in gynephilic girls with gender dysphoria – organizational and activational effects of testosterone. J. Psychiatry Neurosci. *41*, 395–404.

Burrows, S. (2011). The Chevalier d'Eon and His Worlds (London: Bloomsbury).

Carrillo, B., Gómez-Gil, E., Rametti, G., Junque, C., Gomez, A., Karadi, K., Segovia, S., and Guillamon, A. (2010). Cortical activation during mental rotation in male-to-female and female-to-male transsexuals under hormonal treatment. Psychoneuroendocrinology *35*, 1213–1222.

Churchland, P.S., Sejnowski, T.J., (1988). Perspectives on cognitive neuroscience. Science *242* (4879), 741–745.

Cortes, L.R., Carla, D.C., and Forger, N.G. (2019). Does gender leave an epigenetic imprint on the brain? Front. Neurosci. *13*, 173.

Fernández, R., Guillamon, A., Cortés-Cortés, J., Gómez-Gil, E., Jácome, A., Esteva, I., Almaraz, M., Mora, M., Aranda, G., and Pásaro, E. (2018). Molecular basis of gender dysphoria: Androgen and estrogen receptor interaction. Psychoneuroendocrinology *98*, 161–167.

Feusner, J.D., Lidstrom, A., Moody, T.D., Dhejne, C., Bookheimer, S.Y., and Savic, I. (2017). Intrinsic network connectivity and own body perception in gender dysphoria. Brain Image Behav. *11*, 964–976.

Guillamon, A., Junque, C., and Gomez-Gil, E. (2016). A review of the status of brain structure research in transsexualism. Arch, Sex Behav. *45*, 1615–1648.

Hahn, A., Kranz, G.S., Küblböck, M., Kaufmann, U., Ganger, S., Hummer, A., Seiger, R., Spies, M., Winkler, D., Kasper, S., Windischberger, C., Swaab, D.F., and Lanzenberger, R. (2015). Structural connectivity networks of transgender people. Cereb. Cortex *25*, 3527–3534.

Heylens, G., Elaut, E., Kreukels, B.P.C., Paap, M.C.S., Cerwenka, S., Richter-Appelt, H., Cohen-Kettenis, P.T., Haraldsen, I.R., DeCuypere, G. (2014). Psychiatric characteristics in transsexual individuals: Multicentre study in four European countries. Br. J. Psychiatry. *240*, 151–156.

Hulshoff Pol, P.T.C.-K., Van Haren, N.E.M., Peper, J.S., Brans, R.G.H., Cahn, W., Schnack, H.G., Gooren, L.J.G., and Kahn, R.S. (2006). Changing your sex changes your brain: Influences of testosterone and estrogen on adult human brain structure. Eur. J. Endocrinol. *155*, 107–114.

Khan, F.N. (2016). A history of transgender health care. [online] https://blogs.scientificamerican.com/guest-blog/a-history-of-transgender-health-care/.

Kim, T.H., Kim, S.K., and Jeong, G.W. (2015). Cerebral gray matter volume variation in female-to-male transsexuals: A voxel-based morphometric study. Neuroreport *26*, 1119–1125.

Kranz, G.S., Hahn, A., Kaufmann, U., Küblböck, M., Hummer, A., Ganger, S., Seiger, R., Winkler, D., Swaab, D.F., Windischberger, C., Kasper, S., and Lanzenberger, R. (2014). White matter microstructure in transsexuals and controls investigated by diffusion tensor imaging. J. Neurosci. *34*, 15466–15475.

Künzel, H.E., Murck, H., Stalla, G.K., and Steiger, A. (2010). Changes in the sleep electroencephalogram (EEG) during male to female transgender therapy. Psychoneuroendocrinology *36*, 1005–1009.

Luders, E., Sánchez, F.J., Gaser, C., Toga, A.W., Narr, K.L., Hamilton, L.S., and Vilain, E. (2009). Regional gray matter variation in male-to-female transsexualism. Neuroimage *46*, 904–907.

Luders, E., Sánchez, F.J., Tosun, D., Shattuck, D.W., Gaser, C., Vilain, E., and Toga, A.W. (2012). Increased cortical thickness in male-to-female transsexualism. J. Behav. Brain Sci. *2*, 357–362.
Mancini, E. (2010). Magnus Hirschfeld and the quest for sexual freedom. A history of the first international sexual freedom movement (New York: Palgrave Macmillan).
Manzouri, A. and Savic, I. (2018). Possible neurobiological underpinnings of homosexuality and gender dysphoria. Cereb. Cortex *29*, 2084–2101.
Mueller, S.C., De Cuypere, G., and T'Sjoen, G. (2017). Transgender research in the 21st century: A selective critical review from a neurocognitive perspective. Am. J. Psychiatry *174*, 1155–1162.
Perez-Laso, C., Cerdan, S., Junque, C., Gómez, Á., Ortega, E., Mora, M., Avendaño, C., Gómez-Gil, E., Del Cerro, M.C.R., and Guillamon, A. (2018). Effects of adult female rat androgenization on brain morphology and metabolomic profile. Cereb. Cortex *28*, 2846–2853.
Providentia. (2010). Dorchen's Day. [online] https://drvitelli.typepad.com/providentia/2010/12/dorchens-story.html.
Rametti, G., Carrillo, B., Gómez-Gil, E., Junque, C., Segovia, S., Gomez, A., and Guillamon, A. (2011a). White matter microstructure in female to male transsexuals before cross-sex hormonal treatment: A diffusion tensor imaging study. J. Psychiatr. Res. *45*, 199–204.
Rametti, G., Carrillo, B., Gómez-Gil, E., Junque, C., Zubiarre-Elorza, L., Segovia, S., Gomez, A., and Guillamon, A. (2011b). The microstructure of white matter in male to female transsexuals before cross-sex hormonal treatment: A DTI study. J. Psychiatr. Res. *45*, 949–954.
Richards, C, Bouman, W.P., Seal, L., Barker, M.J., Nieder, T.O., and T'Sjoen, G. (2016). non-binary or genderqueer genders. Int. Rev. Psychiatry *28*, 95–102.
Savic I. and Arver, S. (2011). Sex dimorphism of the brain in male-to-female transsexuals. Cereb. Cortex *21*, 2525–2533.
Seiger, R., Hahn, A., Hummer, A., Kranz, G.S., Ganger, S., Woletz, M., Kraus, C., Sladky, R., Kautzky, A., Kasper, S., Windischberger, C., and Lanzenberger, R. (2016). Subcortical gray matter changes in transgender subjects after long-term cross-sex hormone administration. Psychoneuroendocrinology *74*, 371–379.
Schöning, S., Engelien, A., Bauer, C., Kugel, H., Kersting, A., Roestel, C., Zwitserlood, P., Pyka, M., Dannlowski, U., Lehmann, W., Heindel, W., Arolt, V., and Konrad, C. (2010). Neuroimaging differences in spatial cognition between men and male-to-female transsexuals before and during hormone therapy. J. Sex Med. *7*, 1858–1867.
Smith, E.S., Junger, J., Derntl, B., and Habel, U. (2015). The transsexual brain – A review of findings on the neural basis of transsexualism. Neurosci. Biobehav. Rev. *59*, 251–266.
Soleman, R.S., Schagen, S.E., Veltman, D.J., Kreukels, B.P.C., Cohen-Kettenis, P.t., Lambalk, C.B., Wouters, F., and Delemarre-van de Waal, H.A. (2013). Sex differences in verbal fluency during adolescence: A functional magnetic resonance imaging study in gender dysphoric and control boys and girls. J. Sex Med. *10*, 1969–1977.
Sommer, I.E., Cohen-Kettenis, P.T., van Raalten, T., Vd Veer, A.J., Ramsey, L.E., Gooren, L.J., Kahn, R.S., and Ramsey, N.F. (2008). Effects of cross-sex hormones on cerebral activation during language and mental rotation: An fMRI study in transsexuals. Eur. Neuropsychopharmacol. *18*, 215–221.
Uribe, C., Junque, C., Gomez-Gil, E., Abos, A., Mueller, S.C., Guillamon, A., 2020. Brain network interactions in transgender individuals with gender incongruence. NeuroImage *211*, 116613. https://doi.org/10.1016/j.neuroimage.2020.116613.
Watkins, E.S. (2007a). The medicalisation of male menopause in America. Soc. Hist. Med. *20*, 369–388.
Watkins, E.S. (2007b). The Estrogen Elixir: A History of Hormone Replacement Therapy in America (JHU Press), pp. 10. ISBN: 978-0-8018-8602-7.
Zhou, J., Hofman, M., Gooren, L.J., and Swaab, D.F. (1995). A sex difference in the human brain and its relation to transsexuality. Nature *378*, 68–70.
Zubiaurre-Elorza, L., Junque, C., Gomez-Gil, E., Segovia, S., Carrillo, B., Rametti, G., and Guillamon, A. (2013). Cortical thickness in untreated transsexuals. Cereb. Cortex *23*, 2855–2862.
Zubiaurre-Elorza, L., Junque, C., Gomez-Gil, E., and Guillamon, A. (2014). Effects of cross-sex hormone treatment on cortical thickness in transsexual individuals. J. Sex Med. *11*, 1248–1261.

Bionotes

Meltem Kiyar
Department of Experimental Clinical and Health Psychology, Ghent University, Ghent, Belgium

Meltem Kiyar is a PhD student in the Department of Experimental Clinical and Health Psychology at Ghent University, Ghent, Belgium under the supervision of Sven Mueller and Guy T'Sjoen. Her PhD examines the impact of social exclusion on underlying psychophysiology and neurobiology in transgender persons before and during gender-affirming hormone treatment.

Sarah Collet
Department of Endocrinology and Center for Sexology and Gender, Ghent University Hospital, Ghent, Belgium

Sarah Collet is an MD and presently a PhD student in the Faculty of Medicine and Health Science in the Department of Internal Medicine & Pediatrics, Endocrinology at Ghent University Hospital, Ghent, Belgium under the supervision of Guy T'Sjoen and Sven Mueller. Her PhD examines the effect of minority stress on inflammation status and brain structure & function in transgender persons

Guy T'Sjoen
Department of Endocrinology and Center for Sexology and Gender, Ghent University Hospital, Ghent, Belgium

Guy T'Sjoen is an MD and Professor of Endocrinology in the Faculty of Medicine and Health Science in the Department of Internal Medicine & Pediatrics, Endocrinology. He is a founding member of the European Professional Association for Transgender Health (EPATH) and his researchers examines all aspects of transgender health and care.

Sven C. Mueller
Department of Experimental Clinical and Health Psychology, Ghent University, Henri Dunantlaan 2, 9000, Ghent, Belgium
sven.mueller@ugent.be

Sven C. Mueller is a psychologist and Associate Professor at the Department of Experimental Clinical and Health Psychology at Ghent University, Ghent, Belgium and a researcher at the Department of Personality, Psychological Assessment and Treatment, University of Deusto,Bilbao,Spain. His research centers on the effects of stress (social exclusion) on the mental health and underlying neurobiology of transgender persons. In addition, he examines the effect of childhood maltreatment on social and cognitive control processes.