Comprehensive Psychoneuroendocrinology 6 (2021) 100050

Contents lists available at ScienceDirect

Comprehensive Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/cpnec

Psychoneuroendocrine protocol to comprehensively study sexually dimorphic cognition

Sarah Kheloui [a,e,f], Mathias Rossi [a,e,f], Silke Jacmin-Park [b,e,f], Ophélie Larocque [b,e,f], Morgan Vallée [d,e,f], Philippe Kerr [a,e,f], Olivier Bourdon [c,e,f], Robert-Paul Juster [a,e,f,*]

[a] Department of Psychiatry and Addiction, University of Montreal, Montreal, Quebec, Canada
[b] Department of Psychology, University of Montreal, Montreal, Quebec, Canada
[c] Department of Psychology, Université du Québec à Montréal, Montreal, Quebec, Canada
[d] Department of Sociology, Université du Québec à Montréal, Montreal, Quebec, Canada
[e] Centre de recherche de l'Institut universitaire en santé mentale de Montréal, Canada
[f] Center on Sex*Gender, Allostasis and Resilience, Canada

ARTICLE INFO

Keywords:
Sexually dimorphic cognition
Sex differences
Sex hormones
Gender diversity
Sexual orientation

ABSTRACT

Background: A large body of research provides evidence for sex differences in cognitive abilities. These sex differences stem from the interplay between biological sex (e.g., birth-assigned sex, sex hormones) and psychosocial gender (e.g., gender identity, gender-roles, sexual orientation). Literature remains rather mixed with regards to the magnitude of sex and gender effects on cognitive abilities and mental health. Growing evidence shows that sex hormone assessment combined with measures of psychosocial gender may be fundamental to comprehensively understand individual differences in sexually dimorphic cognitive abilities.

Objectives: This study protocol describes a sexually dimorphic cognitive battery to assess the influence of sex hormones on performance. In parallel, we aim to assess the inter-related effects that biological sex and psychosocial gender-based factors exert on cognition and mental health.

Methods: Our projected sample includes 180 adult participants who are at least 18 years old. Sub-groups will be recruited based on birth-assigned sex, gender identity, and sexual orientation. Biological measures will be collected via salivary samples throughout testing to include sex hormones (testosterone, estradiol and progesterone) and stress hormones (cortisol). Demographic and psychosocial variables will be measured through self-report questionnaires. Participants will be required to complete eight classic cognitive tasks that assess a variety of cognitive domains in a 2-h testing session.

Results and future directions: Results from this study provides unique insights into the correlates of cognitive sex differences and gender diversity. This will give us solid ground to further investigate these influences in clinical populations in which sex hormones and cognitive functioning are often altered.

1. Introduction

The sexes differ in their cognitive abilities. Despite decades of research on sexually dimorphic cognition, this research area remains complex and controversial. Many studies have argued that the sexes are more similar than dissimilar as the effect sizes observed are often quite small [59]. In general, women perform better at verbal tasks assessing phonemic fluency [119], verbal working memory [68] and reading abilities [106]. Moreover, women tend to have better social cognitive abilities including facial and emotional recognition [91]. They also perform best at verbal episodic memory tasks whereas men present better spatial episodic memory [54]. For their part, men show better spatial abilities than women in mental rotation and navigational tasks [34,50]. These sex differences in cognitive functions seem to persist throughout life and into older age [74]. Indeed, research among the elderly shows that cognitive decline as a result of aging is greater among men than women in several domains such as perceptomotor speed and integration as well as visuospatial abilities.

Sex differences in cognition are also fundamental in neuropsychiatric conditions as they relate to variability in onsets, prevalence,

* Corresponding author. Department of Psychiatry and Addiction, Faculty of Medicine, Université de Montréal Centre de recherche de l'Institut universitaire en santé mentale de Montréal 7331 Hochelaga Street, H1N 3V2, Montreal, Quebec, Canada.
E-mail address: robert-paul.juster@umontreal.ca (R.-P. Juster).

https://doi.org/10.1016/j.cpnec.2021.100050
Received 27 December 2020; Received in revised form 15 March 2021; Accepted 15 March 2021

symptomatology and cognitive alterations observed. Importantly, the sexes often differ in multiple neuropsychiatric and neurodegenerative conditions such as Alzheimer's disease, autism and schizophrenia [5,39,46]. One hypothesis potentially explaining these differences focuses on the implication of sex hormone variations [4,46]. This evidence justifies the relevance of investigating sex hormone correlates of sexually dimorphic cognition in diverse populations.

1.1. Biological variables

1.1.1. Sex hormones

Sex hormones and their variations have great implications in shaping cognitive sex differences [52]. Nonetheless, there is great within-sex variations which warrant consideration of sex hormone effects on the brain in a dimensional manner rather than a categorical one [51]. In brief, sex hormone influences are exerted in two parts through activational and organizational effects [1]. Organizational effects occur at critical periods (6–12 weeks) of fetal development in which sexual differentiation of the brain occurs [107]. These prenatal processes often expose females and males to different gradients of sex hormone concentration [82]. During this time, the male brain is exposed to androgens which will have defeminizing and masculinizing effects whereas the female brain is protected through the active suppression of androgen exposition [81,82].

Organization sex hormone effects can be disrupted or altered in several situations. For example, Congenital Adrenal Hyperplasia (CAH) is a condition in which individuals are exposed to irregular surges of sex hormones during prenatal development. Those with this condition show a spatial advantage among females [79], demonstrating a masculinized organizational effect. Similarly, prior to gender affirming hormonal therapy, transgender individuals seem to present differential brain activation patterns during cognitive tasks (e.g., verbal fluency) – congruent with their gender identity rather than their birth-assigned sex [80,105]. This may support some organizational effects of sex hormones on gender identity; however, the literature remains rather mixed and further investigations need to be conducted. Despite being permanent, the brain's organization interact with later activational effects that occur during puberty and deactivation effects after reproductive age.

Activational effects are defined as the shaping of behavior and cognitive abilities by time varying circulating sex hormone changes through the lifespan [126]. They can also be observed via hormonal therapy in aging populations. For instance, when administered androgen blockers, men suffering from prostate cancer seem to show lower visuospatial abilities and increased verbal memory [25]. Similarly, for women, they seem to have their verbal abilities enhanced when undergoing hormonal therapy in studies of healthy participants and patients afflicted by Alzheimer's disease [49,127].

Sex hormone exogenous administration also provides great insight into activational effects as they seem to modulate social and cognitive behaviors [21], Evidence shows that women's mental rotation ability is enhanced when administered testosterone [88]. In men, testosterone administration has also been linked to diminished social cognitive abilities whereas estrogen increases emotional reactivity [83]. Interestingly, a meta-analysis showed that *transgender* people undergoing gender affirming hormonal therapy had enhanced cognitive performance in mental rotation and verbal fluency, which is congruent with their gender-identity [63]. For example, female-to-male transgender people performed better than male-to-female transgender people when administered testosterone. Exogenous administration methods, however, present some limitations (ex. time laps and dosage) and results could be influenced by numerous psychosocial variables [21]. Taken together, activational effects on cognitive functions need to be further investigated as reviews seem to show mixed and inconsistent results for both women and men [24,58,74,115] as well as gender diverse people. This highlights the complex nature of the processes underlying cognitive abilities that interact in a dynamic fashion across lifespan development from womb to tomb [107].

Testosterone in men has been shown to vary for circadian, circatrigintan (i.e. 30 day cycle) as well as seasonal rhythms [23,42,104] which seems to modulate their mental rotation performance [84]. Evidence also demonstrates an effect of circulating testosterone on mental rotation as error rates and response time were negatively associated with testosterone levels [57]. Similar results showed that testosterone had positive effects on mental rotation and that this effect varied as a function of age [110]. One study also demonstrated a positive association between testosterone concentrations and mental rotation performance of boys as young as 1–2.5 months old, suggesting organizational effects of sex hormones on cognition [28]. However, androgen's influence in the shaping of boy's and men's cognitive performance present somewhat controversial results. Some results show no associations between testosterone and mental rotation for neither men and women [93]. One twin study also found no correlations between prenatal sex hormones [112]. Moreover, it appears that pubertal testosterone surges were negatively associated with mental rotation performance later on for young adult males [118]. These rather conflicting results could be explained by a myriad of factors such testosterone assessment itself (ex. time varying cycles and metabolic activity), but also the psychometric properties of cognitive tasks [22].

Menstrual cycle variations are also integral to a women's reproductive life and also seems to influence cognition. Progesterone and estradiol levels vary over a 28 day period, but can range between 24 and 38 days for adult women [41]. These hormonal shifts divide the menstrual cycle into two phases. First, the follicular phase that occurs right after menstruation is characterized by low progesterone and estradiol at first and then an increase of estradiol towards the end [98]. Secondly, the luteal phase occurs thereafter and is characterized by relatively low estradiol and an increase in progesterone until the mid-phase followed by a consistent decrease of both sex hormones towards the end of the phase [98]. Interestingly, research has shown that women's performance on verbal and motor tasks are diminished during the mid-luteal phase of their cycle, the phase when estradiol is lowest [72]. Similarly, mental rotation performance is highest during the preovulatory period in which both progesterone and estradiol are low [84]. Moreover, women in the luteal phase use different cognitive strategies in navigational tasks which leads them to perform better [102]. Sustained attention and the ability to discriminate different stimuli is also a cognitive domain that seems to be modulated by menstrual cycle [89]. Despite demonstrating a central role of estrogen and progesterone in cognition and brain functions, results need to be further replicated as they appear to be inconsistent [37,67].

Similarly, oral contraceptives provide additional insights into the assessment of sexually dimorphic cognition. Oral contraceptives have a direct impact on hormonal fluctuations by blocking ovulation. Oral contraceptives vary based on (A) their androgenic activity and (B) their hormonal composition (ex. ethinyl estradiol and progesterone) at different moments of the cycle [29]. While results are inconsistent, women seem to have better verbal memory during the active phase of the contraceptive pill compared to other phases [76]. Furthermore, women using anti-androgenic contraceptives and naturally cycling women show better verbal abilities than women using contraceptives with androgenic properties [8]. These findings strongly highlight the need to consider oral contraception in the study of sexually dimorphic cognition in addition to other medications that can modulate sex hormones.

1.2. Psychosocial variables

1.2.1. Sexual orientation

Sexually dimorphic abilities do not rely solely on sex hormone influences as other factors like gender identity, gender-roles, and sexual orientation may also contribute to inter-individual variability within the sexes even if some studies have found no differences [44]. In general, it appears that gay men have similar performance patterns to heterosexual women and significantly differ from heterosexual men in spatial tasks

and verbal fluency [95,96,124]. This has led to the hypothesis of a cross-sex(gender) shift in cognitive performance for sexual minorities that may be due to early prenatal androgen exposition [96,124]. Sexual orientation and cross-sex(gender) cognitive performance could be a function of organizational effects on the brain [27]. This hypothesis seems supported by results showing that women with CAH present male-like spatial performance and more sexual attraction towards same sex individuals [55,94]. Moreover, a multivariate meta-analysis showed results in support of this hypothesis as sexual minorities presented sex-reversed patterns at both male and female favoring sex-typical spatial tasks [125]. As for lesbian women, they seem to perform according to their birth-assigned sex in some cognitive domains such as spatial memory [20] rather than showing a sex-reversed pattern. The meta-analysis conducted by Ref. [125]; showed that lesbian women performed accordingly to their sex demonstrating patterns similar to heterosexual women – thus confirming previous results. However, this area requires further investigation as some results show that lesbian women have better mental rotation performance compared to heterosexuals [44].

1.2.2. Gender

Gender is defined by the a self-identification and behaviors associated with socio-cultural constructions of sex stereotypes that are classically associated with femininity and masculinity [92]. This definition rose from the necessity to disentangle social implications from biological ones in the shaping of masculinity and femininity which has been espoused by feminist academics [61]. This shift has contributed to the ongoing debate between evolutionary perspectives and feminist scholars regarding the study of male and female sex differences [18,35]. Gender as opposed to sex, would not be binary, but rather fluid and better illustrated on a dimensional scale rather than a categorical one. Beyond this position, gender can be better defined as the manner by which societies and cultures build psychosocial attributes based upon biological sex [30].

Gender can be sub-divided into many sub-facets such as gender identity (i.e., personal identification to one's gender) and gender-roles (i.e., attitudes and behaviors enacted as a function of one's gender identity). Gender schema theory proposes that the sexes internalize social norms associated with femininity and masculinity and mimic those behaviors/attitudes in order to remain coherent with their self-perception [10,13,30,32]. This integration process leads to the perpetuation of social stereotypes thus generating the differences we may observe between the sexes in multiple domains (ex. cognitive abilities). Moreover, according to this theory, the gender-self can develop itself in non-binary categories (i.e. androgynous and undifferentiated) [9]. This led to the development of the Bem Sex-Role Inventory [11]. Despite many critics due to evolving gender-role conceptualizations [33], this instrument remains an instrument that greatly shaped our thinking about gender [70].

According to gender schema theory, social norms and gender-identification effect cognitive abilities [77,78]. Evidence suggest that gender-role identification may mediate sex-typed cognitive performance when it matches birth-assigned sex [99]. For example, verbal and spatial abilities would then be increased when gender-roles are consistent with sex. However, this has yet to be conclusively determined as some studies show that cognitive performance is more accurately predicted by sex rather than by gender-role identification [64]. Moreover, one study showed that women believing that their mathematical performance was driven by biological factors scored lower than women believing their performance was influenced by social factors [31]. This suggests that social implications are central to a better understanding of sexually dimorphic cognition.

1.3. Rational for project proposal

In sum, sexually dimorphic cognition seems to be influenced by a myriad and multiplicity of biological and psychosocial variables. However, few studies have determined the extent and manner by which each sex- and gender-based factor is related to cognitive performance. Specifically, the study of sex hormone implications on cognition and its relation to mental and physical health in different populations representing diversity in sex, gender, and sexual orientation is highly warranted. Indeed, only a handful of recent studies began to look at this research question using a transdisciplinary approach. To further advance this area, the current project protocol aims to better understand the underlying sex and gender mechanisms driving cognitive sex differences in men, women, and gender diverse people. In a sample of 180 participants, a cognitive battery consisting of classic tasks that present sex differences as well as some that do not will be administered. All variables of significance to the rationale of our study will be accounted for; namely, sex hormones, oral contraception, menstrual cycle, reproductive milestones, sexual orientation, gender identity, and gender-roles to name a few.

1.4. Objectives and hypothesis

1.4.1. Objectives

1.4.1.1. Objective (1). The first objective of this study is to assess whether a comprehensive battery of classic cognitive tasks are still sexually dimorphic or not and how performance is influenced by sex hormones. The focus of this objective is identifying the effect magnitude of sex hormone modulation, which represents an elegant approach to study sex as a dimension rather than as a category. Our study will be considered unsuccessful if only sex was a predictor of cognitive performance. The validation of the most significant tasks would give us the opportunity to administer subsets of this battery in different contexts (e.g., brain imaging environment). Lastly, the next goal of applying our protocol will be to study clinical populations (e.g., psychosis) in which a link between sex hormones is observed [17,46], therefore strengthening our understanding of sex hormones, cognitive functioning, and mental health.

1.4.1.2. Objective (2). The second objective of this study is to delineate the effects of multiple psychosocial variables like gender identity, gender-roles, and sexual orientation over and above the effects of birth-assigned sex and sex hormones in explaining sexually dimorphic cognitive performance.

1.4.2. Hypothesis

1.4.2.1. Hypothesis (1). Firstly, we hypothesize that cognitive performance will present sex-specific differences. For instance, we expect women to perform better than men at emotional recognition tasks, verbal memory, verbal fluency and fine motor skill tasks. As for men, we expect that they will perform better than woman at mental rotation and visuo-spatial tasks.

1.4.2.2. Hypothesis (2). Secondly, we expect that sex by gender interactions will correlate with cognitive functions. Therefore *(2a)*, we postulate a positive correlation between femininity traits and sex-typed feminine tasks. Hence, people who highly identify to feminine traits (e.g., feminine gender identity, feminine gender roles) will perform better on sex-typed feminine tasks. The same goes for individuals who score highly on the masculinity traits for sex-typed masculine tasks. Moreover *(2b)*, we expect to observe a sex(gender)-shift in cognitive performance when considering sexual orientation. Consistent with the literature, we expect gay men and heterosexual women to perform in a similar way and lesbian women to perform similarly to heterosexual men. In addition to this *(2c)*, we hypothesize that gender identity will modulate the cognitive performance of transgender and gender diverse people. In this manner, we expect them to perform in a similar fashion to the gender they identity with when compared to cisgender people (e.g.,

people identifying themselves in accordance with their birth-assigned sex).

1.4.2.3. Hypothesis (3). Thirdly, we hypothesize that *(3a)* sex hormones (testosterone, estradiol and progesterone) will present sex-specific hormonal profile differences. Moreover, *(3b)* we expect sex hormones to be significant predictors of cognitive functioning over and above those of gender variables. In this manner, we expect positive correlations between sex hormone levels and the different cognitive domains in correspondence. That is, estradiol and progesterone will be positively associated with female-typic cognitive abilities while testosterone will be positively associated with male-typic cognitive abilities. Lastly, *(3c)* we expect menstrual cycle to influence hormonal profiles as well as cognitive performance with women performing better at male-favoring tasks when estradiol is low (i.e., mid-luteal phase). Inversely, for the female favoring tasks, we expect women to perform better when estrogen is highest (i.e., follicular phase).

2. Methods

2.1. General overview

This research program will be conducted by Robert-Paul Juster's newly established Centre on Sex*Gender, Allostasis, and Resilience (CESAR) based at the Centre de recherche de l'Institut universitaire en santé mentale de Montréal (CRIUSMM) that is affiliated with the University of Montreal. This research project was approved by the Scientific and Ethical Committees of the Centre intégré universitaire de santé et de services sociaux de L'Est-de-l'Île-de-Montréal. This study aims to deepen scientific knowledge on the underlying biological (e.g., birth-assigned sex and sex hormones) and psychosocial mechanisms (e.g., sexual orientation, gender identity, gender-roles) involved in sexually dimorphic cognition.

We will apply a transdisciplinary lens that will allow us to capture the complexity of factors implicated in cognitive functions by integrating numerous factors implicated in cognitive functions. This holistic approach views cognition as an ensemble in which all the sex- and gender-based components that structure it are inter-related. This approach provides us with great empirical strength with potential clinical significance in the future. The implications that sex hormones have on cognition and its relation to mental and physical health in different populations remains a relatively unexplored area that we wish to contribute towards. For one, the sexes and genders are known to be affected differently in a variety of neuropsychiatric and neurodegenerative disorders such as schizophrenia and Alzheimer's disease [39,46].

Moreover in the context of hormonal therapies, the study of transgender and gender diverse people who often experience hormonal changes appears to be associated with cognitive changes [80]. Taken together, a better understanding of the influence that sex hormones have on cognition is complemented by including psychosocial variables and measures related to gender affirming hormone therapies as well as reproductive information for all participants. Ultimately, we will provide greater insights on mechanisms and ways to tailor care with consideration of sex and gender diversity in a person-centered manner.

2.2. Study design

This quasi-experimental correlational study will be conducted in approximately 2 h and its chronology, measures and timepoints are presented in the protocol visualization (see Fig. 1). Upon their arrival, participants will complete and sign the consent form. Our team will answer any questions they may have regarding their participation or the protocol. Testing will occur between 1PM and 5PM to control for diurnal variations. Psychosocial variables will be assessed via self-report questionnaires after testing using standard questionnaires.

Through the testing paradigm, eight tasks that evaluate various cognitive abilities will be administered. The manner in which cognitive tasks will be administered was arranged to prevent interference among the different cognitive faculties required for each task. For instance, one verbal task requires memorization which could be altered with the retrieval of other information if another verbal task was assessed in a temporally short scale. This is the reason we intend on counterbalancing the solicitation of verbal abilities via spatial tasks and vice-versa. Biological measures will be collected at three different timepoints (baseline, mid-point, and at the end) via saliva samples and will include sex hormones (testosterone, estradiol, progesterone) and the stress hormone cortisol.

The assessment of cortisol is justified by the fact that its secretion can influence a large number of cognitive abilities such as memory and attention [19,36,71]. More importantly, a large number of evidence demonstrate sex differences in stress reactivity patterns [2]. These differences seem to be influenced by sex hormones [53] via neurotransmission and activation of brain receptors [86]. For instance, estrogen is known to exacerbate hypothalamic-pituitary-adrenal axis (HPA) activity whereas androgens seem to decrease its activity [53]. Sex hormones also seem to possess organizational and activational effects on the HPA axis in the adolescent brain [48]. Nonetheless, both neuroendocrine systems interact in a dynamic and complementary manner. For example, glucocorticoids seem to contribute the releasing of gonadotropins stimulating factors [100]. In parallel, one study found an interaction effect of cortisol

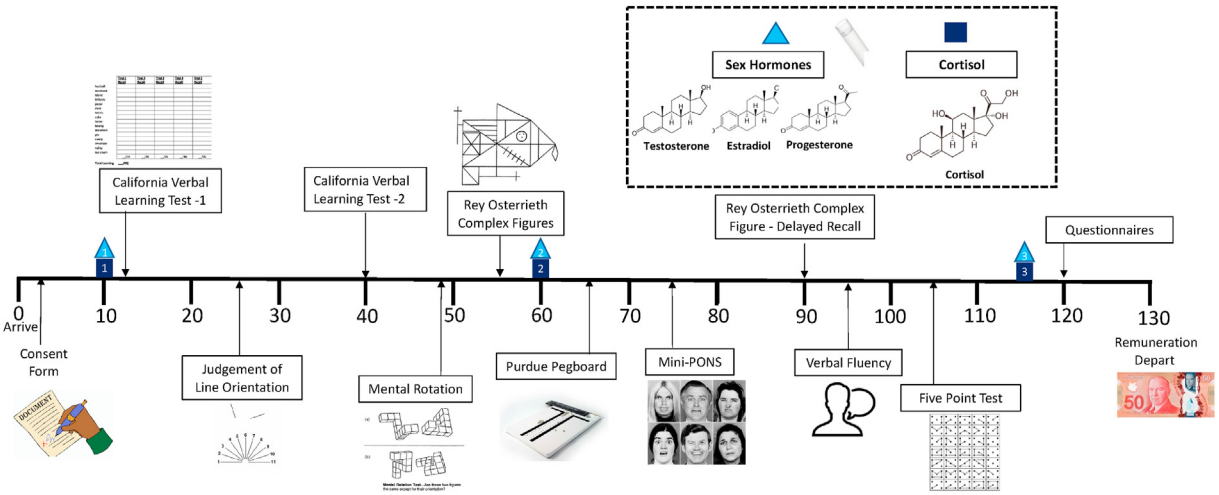

Fig. 1. Study protocol.

and testosterone on hippocampal volumetry as well as cognition (i.e., episodic memory) among men [87]. Indeed, a neuroprotective role of testosterone, larger hippocampal volume and enhanced episodic memory were observed when both testosterone and cortisol were high.

2.3. Sample characteristics

In this project, we aim to recruit 180 men, women, and gender diverse people (e.g., non-binary, gender fluid, queer, transgender people) who live in the greater Montreal area. Groups will be divided based on their birth-assigned sex, gender identity, and sexual orientation which are the main independent variables of interest (see Fig. 2). The gender diverse group is not divided based on their sexual orientation as their gender identity will be the predominant factor when conducting our group comparisons analysis. Moreover, sexual orientation can be non-binary for gender diverse individuals which would necessitate us to create multiple groups that lowers power.

Participants will need to be fluent either in English or in French since all the tests are procured in both official Canadian languages. The minimal age to participate in the study will be set at 18 years old and we will not have an age limit in order to provide insights into age-based variation. Indeed, since we will be focusing on sex hormones, we plan on recruiting participants from a wide age range to inform future research directions. This will give us the opportunity to determine the effects of hormonal variations on cognitive functioning through the lifespan.

Exclusion criteria will include severe mental and/or physical health issues which can severely impair cognitive functioning such as neuroendocrine diseases, brain injuries or neuropsychological conditions. A screener will be used to account for a wide-variety of health conditions rather than as exclusionary criteria. Our liberal inclusion criteria have been chosen in order to maximize representation of sexual and gender minorities since they are often underrepresented. We therefore strive towards a more inclusive recruitment strategy that will measure confounders rather than using them to exclude people. Participants will be remunerated with 50 CAD.

Data will be collected and stored respecting the Tri-Council Policy Statement for Research Involving Humans as well as the Helsinki Declaration. Screener and contact information will be kept private and only members of the research team that completed all the necessary ethical training will be allowed to access data, oversee participant scheduling and contact participants. Participants' contact information will be connected to a participant ID number generated for the purpose of this study, which will serve as a connection between participant data and identifying information and therefore guarantee the confidentiality of the participants.

2.4. Recruitment

Recruitment will be a two-phased process. Firstly, we will establish community partnerships that will facilitate recruitment of the LGBTQ + people at different ages. In doing so, our team is currently conducting individual qualitative interviews with members of the transgender and gender diverse community whereby we are discussing determinants of health research while introducing our research methodologies for psychoneuroendocrine approaches. We share with our interviewees our protocol which is a crucial step that gives us the opportunity to assess the acceptability of our methodology. More importantly, this generates visibility and transparency of our research project within the community and will be of great help in the second phase of our recruitment process.

Secondly, we will start recruiting participants via printed and electronic advertisements as well as social media. We have also contacted a number of LGBTQ + organizations that have accepted to distribute our flyer information within their respective networks. Recruitment will be conducted on a voluntary basis. Potential recruits will be invited to contact the *CESAR* laboratory for a screening interview prior to scheduling appointments which will permit us to determine the eligibility of the participants.

Since several variables could interfere with cognitive functioning, we will collect information regarding psychiatric history as well as physical and mental health. In addition, information on hormonal milieu and reproductive milestones (e.g., age of menarche, age when starting gender affirming hormonal therapies) will be ascertained by assessing contraception and medication intake in the screening questionnaire which is particularly relevant for transgender people undergoing hormonal therapy. Similarly, sociodemographic variables (e.g., education, civil status, age, race/ethnicity) will also be assessed via the screening questionnaire. When participants will be retained for the study, an appointment will be scheduled with them in the afternoon.

2.5. Material and methods

2.5.1. Psychosocial measures

Psychosocial measures such as sexual orientation, gender identity, and gender-roles will be assessed via self-report questionnaires. Similarly, we will account for other variables that can potentially influence cognitive performance such as general mental health status measuring psychological and social well-being. Questionnaires characteristics and information are resumed in Table 1.

2.5.2. Biological measures

We will determine the effect of sex hormones on participants' cognitive participant by assessing testosterone, estradiol and progesterone samples. Saliva samples destined for assaying of these sex hormones will be taken for each participant at the beginning and end, mid-point, and end of the testing session (see Fig. 1). In addition, the influence of stress on sex hormones and some cognitive functions will be controlled for if needed.

2.5.2.1. Data management. Sterilized 5 mL 57 × 15.3 mm screw cap tubes (Sarstedt, Item No. 62.558.201) will be used to collect 2 mL of saliva guided with thick straws. Assays will be conducted at Sonia Lupien's Saliva Laboratory of the CRIUSMM. Upon storage in −20° Celsius freezers, frozen samples will be brought to room temperature to then be centrifuged at 1500×*g* (3000 rpm) for a total of 15 min. Subsequently, all assays will be run in duplicates and then averaged. We will use high-sensitivity enzymeimmune assays for cortisol (Salimetrics®, No. 1–3102, sensitivity: 0.012–3 μg/dl), estradiol (Salimetrics®, No. 1–3702, sensitivity: 1–32 pg/ml), and progesterone (Salimetrics®, No.1–1502, sensitivity: 5 pg/ml). As for testosterone, it will be determined by expanded-range enzymeimmune assay (Salimetrics®, No. 1–2402,

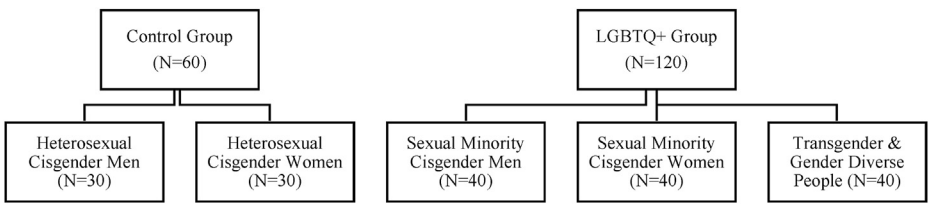

Fig. 2. Groups and subgroups division.

Table 1
Questionnaires characteristics.

Title	Description
MHC-SF Mental Health Continuum – Short Form [66]	• Measures emotional, psychological, and social well-being. • 14 Items.
STA1-Y1 State and Trait Anxiety Inventory [62]	• Measures of the presence and severity of anxiety symptoms and a propensity to be anxious. • 40 Items
BDI Beck Depression Inventory II [7, 62]	• Measures of depression severity • 21 Items
MBI Masclach Burnout Inventory [73]	• Measures three components of the burnout syndrome (i.e. emotional exhaustion, depersonalization, and reduced personal accomplishment) • 22 Items
BSRI-L Bem Sex Role Inventory – Short Form [12,56]	• Measures of femininity and masculinity • 30 Items
KSS Kinsey Homosexual-Heterosexual Rating Scale [108]	• Measures of sexual orientation on a continuum of heretosexuality and homosexuality (0–6)
BASGI Birth Assigned Sex and Gender Identity [6]	• Multidimensional measures of sex and gender-identity • 10 Items

sensitivity: 1 pg/ml). Inter-assay and intra-assay coefficients of variance will be determined for each hormone. Assays will then be duplicated and averaged.

Taking three measures at different timepoints will give us the opportunity to assess baseline and dynamic levels in our secondary analyses. Analytically, enzyme immunoassays (EI) present some limitations as it appears to magnify testosterone when in lower concentrations and to present small associations with liquid chromatography tandem mass spectrometry samples (LC-MS-MS) [109,120]. Moreover, correspondence between EI and LC-MS-MS was stronger when more storage and handling variability methods was inducted which supports the limitations of EI's [90]. While LC-MS-MS's use should be prioritized when assessing hormones [90], we chose to conduct our analysis using EI's for cost saving purposes. However, in interest of transparency, we acknowledge the limitations and unreliability these assays will detail methodological information in forthcoming papers discussing the results of this study.

2.5.3. Cognitive assessment

2.5.3.1. California verbal learning test. The California Verbal Learning Test Second-Edition is a task that evaluates verbal memory. This test takes 30 min including the testing and the delay period. It has been generally shown that women generally perform better than men and that age is more negatively correlated to performance for men [47]. Test-retest reliability coefficients of this edition is good as it ranges between 0.61 and 0.73 for the alternate form and 0.80–0.84 for the standard form in healthy subjects [123]. As for clinical populations, coefficients vary from 0.54 to 0.89 [14].

2.5.3.2. Benton judgement of line orientation. The Benton Judgement of Line Orientation is a task to measure visuospatial judgement divided in two alternate forms (V–H) which requires the participant to match line orientations with different angled lines [15]. The administration time is about 15 min. Men generally outperform women [113] and gay men seem to perform less then heterosexual men [97]. The test-retest reliability is around 0.91 which is high [75].

2.5.3.3. Shepard and metzler. The Shepard and Metzler is a classic measure of mental rotation requiring the ability to transform objects in different angles while using an object reference [103]. The administration time is around 5 min. Men consistently perform better than women [50] and that this effect may be magnified when integrating a time constraint [117]. An almost perfect correlation between the stimuli rotation angles and the identifying matches time has been previously found [116]. Reliability is good with an internal consistency of 0.88 [122].

2.5.3.4. Rey-osterrieth complex figures test. The Rey-Osterrieth Complex Figures Test measures non-verbal memory in which the participants are asked to replicate a figure first by copying it and then drawing it from memory [85]. The test can be completed between 10 and 15 min. Performance appears to be function of sex with men generally performing better, but also age and IQ dependant [43]. Psychometric properties are acceptable as test-retest reliability ranges from between 0.60 and 0.76 and intra- and inter-rater reliability lies between 0.91 and 0.98 [16].

2.5.3.5. Purdue pegboard. The Purdue Pegboard is a task evaluating manual coordination and fine motor skills in which participants are asked to insert metal pieces in two parallel rows containing both 25 holes [111]. The administration time for this task is around 10 min. Women have been shown to generally perform better than men [65]. The psychometric properties of this test are acceptable as validity coefficients ranges between 0.70 and 0.76 whereas reliability lies between 0.63 and 0.76 [111].

2.5.3.6. Short version of the Profile of Nonverbal Sensitivity Test. The Short version of the Profile of Nonverbal Sensitivity Test derived from an original and longer version, will be used to assess emotional recognition [3] via video items containing verbal and non-verbal cues such as face expression, voice, gestures and body posture. The task can be completed in an approximately 15 min time period. Women generally perform better than men [3]. It has an acceptable test-retest reliability of 0.64 [3].

2.5.3.7. Controlled oral word association. The Controlled Oral Word Association task will determine verbal fluency abilities. Participants are given words and instructed to orally generate as many words as possible as a function of the semantic (ex. animal, fruit or vegetable) or phonetic similarities. The administration time is of approximately 10 min. Women have consistently been shown to perform better than men [69]. The test-retest reliability lies is 0.75 and the internal consistency is 0.83 [101].

2.5.3.8. Five point test. The Five Point Test is a standardized measure of non-verbal fluency and executive functioning [114]. The participant is presented with 35 identical squares containing five symmetrically disposed dots and are asked to generate as many designs as possible by connecting the dots. The task takes about 10 min to complete. No clear sex differences have been demonstrated, but a age and education effect has been found showing that performances decreased with age and increased with education level [45]. Reliability measures are good as the test has an internal consistency of 0.80 and a test-retest coefficient of 0.78 [38].

2.6. Statistical analysis

All data analysis will be completed using the Statistical Package for the Social Science Version 25 for Macintosh. Firstly, multivariate analysis of variance (i.e., multiple dependent variables) will be conducted to determine whether group differences exist or not for all cognitive tasks on global scores based. Our main variables of interest as factors include birth-assigned sex and gender identity. Secondly, student t-tests will be used to compare women's cognitive performance based on menstrual cycle phase (luteal/follicular) as well as contraceptive use. Thirdly, we will conduct a two-way multivariate analysis of covariance to determine statistical differences for all cognitive tasks based on sex and gender

while controlling for sexual orientation. This will allow us to group differences an whether there is an interaction effect. and Bonferronni correction will be used when necessary in order to control for multiple comparisons. Moreover, we will conduct sex-disaggregated multiple regressions analysis to evaluate the extent to which biological and psychosocial factors explain sexually dimorphic cognition in a hierarchical, sex-specific manner. The hierarchy will first include sex hormones, followed by sexual orientation and then psychosocial gender (gender identity, gender-roles). We will also integrate covariates in our model such as cortisol, contraception, menstrual cycle, age, education and smoking/drinking habits whenever appropriate. This will give us the opportunity to assess the percentage of explained variance for each additional variable we integrate in the model.

When designing our study protocol, we completed an *a priori* power analyses in order to determine the sample size necessary to conduct our study based on our main analyses. Firstly, in order to detect a small to medium group differences effect [26] at a 80% power for both main and interactions effects, a sample between 104 and 160 participants was required. For the hierarchical regression model, a sample size of $N = 103$ to $N = 152$ was needed to detect sex effects over and above 10 to 14 additional factors while explaining 10% of the variance at 80% power. Consequently, our projected sample of $N = 180$ is appropriate. Effect sizes were chosen based on literature results showing that cognitive sex differences effect sizes generally oscillated between small and medium [59,60].

3. Discussion

The main purpose of this study is to delineate the different influences of biological sex (birth-assigned sex, sex hormone variations) and psychosocial gender (gender identity, gender roles, sexual orientation) factors in the functioning of sexually dimorphic cognition. This is of great empirical value as studies evaluating the correlates of cognitive sex differences are mixed and controversial. In addition, determining the specific influences sex hormones have on cognitive functions gives us a better insight on how to approach cognitive alterations in relation to sex hormones in multiple mental conditions. This is especially pertinent since there is growing evidence of sex hormones are a critical factor in treatments [40].

3.1. Covariates and limitations

Covariates include all potential confounding factors that may interfere with cognitive functions and/or sex hormone levels. They include cortisol, oral contraception, menstrual cycle, age, education, smoking/drinking habits, mental and physical conditions. These will be accounted for in the recruitment process and controlled for where appropriate when conducting our analysis. As for menstrual cycle, which is a critical variable of interest, we will use self-reported measures via cycle history questions. However, as subjective measures can be quite unreliable. We will therefore explore combining these with urinary ovulation kits to strengthen the robustness of our assessment [121]. Because providing urinary samples be a sensitive activity for some individuals, we will emphasize the fact that this is optional.

This research protocol assesses multiple cognitive domains that can be impaired by multiple potential confounding variables such as mental health status (ex. depression and anxiety). These will be assessed via the screening questionnaire and adjusted for in our statistical models. Moreover, we will administer in total eight cognitive tasks over an approximately 2 h period which is quite comprehensive. This can potentially induce fatigue especially since cognitive assessment is demanding. This is the reason why we intend on encouraging participants to take breaks between tasks to attenuate potential fatigue that they may experience.

Stress upon arrival to our laboratory may be a confounding factor influencing cortisol levels and thus affecting sex hormone levels [100]. Hence, we integrated an approximately 10–15 delay in our protocol in order to give proper time for the participant to install themselves and familiarize themselves with the testing environment. A large number of individuals composing it will belong to the LGBTQ + community (n = 120) which is in fact the majority of our total sample. Therefore, one important limit of our study consists in the generalization of its sample to the general population in which sexual and gender minorities are usually underrepresented.

4. Conclusions

This research program allows us better understand how cognition is influenced by sex and gender factors. It has great empirical value since better understanding the influence of sex hormones and gender on cognition opens the door to more in-depth knowledge of different physical and mental health conditions where cognition is altered, such as neuropsychiatric conditions. Finally, the implications that sex hormones have in cognition and its relations to brain functional activity in different populations remains a relatively unexplored area.

Credit Authorship and Contribution Statement

Sarah Kheloui: Term, Conceptualization, Funding acquisition, Methodology, Writing – original draft, Writing – review and editing, Visualization. **Mathias Rossi**: Methodology, Writing – original draft, Writing – review and editing. **Silke Jacmin-Park**: Methodology, Writing – review and editing. **Ophélie Larocque**: Methodology, Writing – review and editing. **Philippe Beauchamp-Kerr**: Writing – review and editing. **Olivier Bourdon**: Writing – review and editing. **Robert-Paul Juster**: Term, Conceptualization, Funding acquisition, Methodology, Writing – original draft, Writing – review and editing, Visualization, Supervision.

Ethical statement

This research project was approved by the local Research Ethics and Scientific boards and adheres with the Declaration of Helsinki. Each participant will provide written and informed consent prior to participation in this study.

Funding

This research project is supported by the Natural Sciences and Engineering Research Council of Canada Discovery grant as well as an Internal Pilot Project grant from the Centre de recherche de l'Insitut universitaire en santé mentale de Montréal both awarded to R.P. Juster. R.P. Juster also holds a Canadian Institutes of Health Research (CIHR) Sex and Gender Science Chair and receives salary support from the Research Scholar Junior 1 award from the Fonds de Recherche du Québec Santé. R.P. Juster and S. Kheloui also have salary support from the Foundation of the Montreal Mental Health University Institute (Institut universitaire en santé mentale de Montréal) and S. Kheloui was granted a CIHR Master's Frederick Banting and Charles Graduate Scholarship.

Declaration of competing interest

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

References

[1] A.P. Arnold, The organizational-activational hypothesis as the foundation for a unified theory of sexual differentiation of all mammalian tissues, Horm. Behav. 55 (2009) 570–578.
[2] T.L. Bale, C.N. Epperson, Sex differences and stress across the lifespan, Nat. Neurosci. 18 (2015) 1413–1420.

[3] T. Banziger, K.R. Scherer, J.A. Hall, R. Rosenthal, Introducing the MiniPONS: a short multichannel version of the profile of nonverbal sensitivity (PONS), J. Nonverbal Behav. 35 (2011) 189–204.
[4] S. Baron-Cohen, B. Auyeung, B. Norgaard-Pedersen, D.M. Hougaard, M.W. Abdallah, L. Melgaard, A.S. Cohen, B. Chakrabarti, L. Ruta, M.V. Lombardo, Elevated fetal steroidogenic activity in autism, Mol. Psychiatr. 20 (2015) 369–376.
[5] S. Baron-Cohen, R.C. Knickmeyer, M.K. Belmonte, Sex differences in the brain: implications for explaining autism, Science 310 (2005) 819–823.
[6] G.R. Bauer, J. Braimoh, A.I. Scheim, C. Dharma, Transgender-inclusive measures of sex/gender for population surveys: mixed-methods evaluation and recommendations, PloS One 12 (2017).
[7] A.T. Beck, R.A. Steer, R. Ball, W.F. Ranieri, Comparison of beck depression inventories-IA and -ii in psychiatric outpatients, J. Pers. Assess. 67 (1996) 588–597.
[8] A.M. Beltz, E. Hampson, S.A. Berenbaum, Oral contraceptives and cognition: a role for ethinyl estradiol, Horm. Behav. 74 (2015) 209–217.
[9] Bem, Utility of alternative procedures for assessing psychological androgyny, J. Consult. Clin. Psychol. 45 (1977) 196–205.
[10] Lenney Bem, Sex typing and the avoidance of cross-sex behavior, J. Pers. Soc. Psychol. 33 (1976) 48–54.
[11] S. Bem, Bem sex role inventory: professional manual, in: C.P. Press (Ed.), Palo Alto, CA, 1981.
[12] S.L. Bem, Bem sex-role inventory: professional manual.. CA, Consulting Psychologists Press, Palo Alto, 1981b.
[13] S.L. Bem, Gender schema theory - a cognitive account of sex typing, Psychol. Rev. 88 (1981c) 354–364.
[14] R.H.B. Benedict, Effects of using same- versus alternate-form memory tests during short-interval repeated assessments in multiple sclerosis, J. Int. Neuropsychol. Soc. 11 (2005) 727–736.
[15] A.L. Benton, N.R. Varney, K.D. Hamsher, Visuospatial judgment - clinical test, Arch. Neurol. 35 (1978) 364–367.
[16] D.T. Berry, R.S. Allen, F.A. Schmitt, Rey-Osterrieth Complex Figure: psychometric char- acteristics in a geriatric sample, Clin. Neuropsychol. 5 (1991) 143–153.
[17] N.A. Brzezinski-Sinai, A. Brzezinski, Schizophrenia and sex hormones: what is the link? Front. Psychiatr. 11 (2020) 693.
[18] D.M. Buss, D.P. Schmitt, Evolutionary psychology and feminism, Sex. Roles 64 (2011) 768–787.
[19] M.G. Calvo, A. Gutiérrez-Garcia, Chapter 16-Cognition and Stress, Stress: Concepts, Cognition, Emotion, and Behavior, Academic Press, 2016, pp. 139–144.
[20] M.R. Canovas, J.M. Cimadevilla, Sexual orientation and spatial memory, Psicothema 23 (2011) 752–758.
[21] J.M. Carré, B.A. Robinson, Testosterone administration in human social neuroendocrinology: past, present, and future, Horm. Behav. 122 (2020), 104754.
[22] P. Celec, D. Ostatníková, J. Hodosy, On the effects of testosterone on brain behavioral functions, Front. Neurosci. 9 (2015).
[23] P. Celec, D. Ostatnikova, Z. Putz, J. Hodosy, P. Bursky, L. Starka, R. Hampl, M. Kudela, Circatrigintan cycle of salivary testosterone in human male, Biol. Rhythm. Res. 34 (2003) 305–315.
[24] M.M. Cherrier, Androgens and cognitive function, J. Endocrinol. Invest. 28 (2005) 65–75.
[25] M.M. Cherrier, A.L. Rose, C. Higano, The effects of combined androgen blockade on cognitive function during the first cycle of intermittent androgen suppression in patients with prostate cancer, J. Urol. 170 (2003) 1808–1811.
[26] J. Cohen, Statistical Power Analysis for the Behavioral Sciences, second ed., L. Erlbaum Associates, Hillsdale, N.J, 1988.
[27] M.L. Collaer, M. Hines, Human behavioral sex differences: a role for gonadal hormones during early development? Psychol. Bull. 118 (1995) 55–107.
[28] M. Constantinescu, D.S. Moore, S.P. Johnson, M. Hines, Early contributions to infants' mental rotation abilities, Dev. Sci. 21 (2018) e12613.
[29] D.B. Cooper, H. Mahdy, Oral contraceptive pills. StatPearls publishing, Treasure Island (FL) (2020).
[30] M. Crawford, R. Chaffin, L. Fitton, Cognition in social-context, Learn. Indiv Differ 7 (1995) 341–362.
[31] I. Dar-Nimrod, S.J. Heine, Exposure to scientific theories affects women's math performance, Science 314 (2006), 435–435.
[32] K. Deaux, B. Major, Putting gender into context - an interactive model of gender-related behavior, Psychol. Rev. 94 (1987) 369–389.
[33] K. Donnelly, J.M. Twenge, Masculine and feminine traits on the Bem sex-role inventory, 1993-2012: a cross-temporal meta-analysis, Sex. Roles 76 (2017) 556–565.
[34] I. Driscoll, D.A. Hamilton, R.A. Yeo, W.M. Brooks, R.J. Sutherland, Virtual navigation in humans: the impact of age, sex, and hormones on place learning, Horm. Behav. 47 (2005) 326–335.
[35] A.H. Eagly, W. Wood, The nature-nurture debates: 25 Years of challenges in understanding the psychology of gender, Perspect. Psychol. Sci. 8 (2013) 340–357.
[36] P.D. Evans, C. Fredhoi, C. Loveday, F. Hucklebridge, E. Aitchison, D. Forte, A. Clow, The diurnal cortisol cycle and cognitive performance in the healthy old, Int. J. Psychophysiol. 79 (2011) 371–377.
[37] M.A. Farage, T.W. Osborn, A.B. MacLean, Cognitive, sensory, and emotional changes associated with the menstrual cycle: a review, Arch. Gynecol. Obstet. 278 (2008) 299–307.
[38] A.L. Fernandez, M.A. Moroni, J.M. Carranza, N. Fabbro, B.K. Lebowitz, Reliability of the five-point test, Clin. Neuropsychol. 23 (2009) 501–509.
[39] M.T. Ferretti, M.F. Iulita, E. Cavedo, P.A. Chiesa, A. Schumacher Dimech, A. Santuccione Chadha, F. Baracchi, H. Girouard, S. Misoch, E. Giacobini, H. Depypere, H. Hampel, P. Women's Brain, I. the Alzheimer Precision Medicine, Sex differences in Alzheimer disease - the gateway to precision medicine, Nat. Rev. Neurol. 14 (2018) 457–469.
[40] A.D. Fisher, J. Ristori, M. Maggi, Pharmachosexology: use of sex hormones in psychiatric conditions, in: E.A. Jannini, A. Siracusano (Eds.), Sexual Dysfunctions in Mentally Ill Patients, Springer International Publishing, Cham, 2018, pp. 215–224.
[41] I.S. Fraser, H.O.D. Critchley, M. Broder, M.G. Munro, The FIGO recommendations on terminologies and definitions for normal and abnormal uterine bleeding, Semin. Reprod. Med. 29 (2011) 383–390.
[42] H. Gall, H.J. Glowania, M. Fischer, [Circadian rhythm of testosterone level in plasma. I. Physiologic 24-hour oscillations of the testosterone level in plasma], Andrologia 11 (1979) 287–292.
[43] C. Gallagher, T. Burke, Age, gender and IQ effects on the Rey-Osterrieth complex figure test, Br. J. Clin. Psychol. 46 (2007) 35–45.
[44] B.A. Gladue, W.W. Beatty, J. Larson, R.D. Staton, Sexual orientation and spatial ability in men and women, Psychobiology 18 (1990) 101–108.
[45] S. Goebel, R. Fischer, R. Ferstl, H.M. Mehdorn, Normative data and psychometric properties for qualitative and quantitative scoring criteria of the Five-point Test, Clin. Neuropsychol. 23 (2009) 675–690.
[46] A. Gogos, L.J. Ney, N. Seymour, T.E. Van Rheenen, K.L. Felmingham, Sex differences in schizophrenia, bipolar disorder, and post-traumatic stress disorder: are gonadal hormones the link? Br. J. Pharmacol. 176 (2019) 4119–4135.
[47] L.V. Graves, C.C. Moreno, M. Seewald, H.M. Holden, E.J. Van Etten, V. Uttarwar, C.R. McDonald, L. Delano-Wood, M.W. Bondi, S.P. Woods, D.C. Delis, P.E. Gilbert, Effects of age and gender on recall and recognition discriminability, Arch. Clin. Neuropsychol. 32 (2017) 972–979.
[48] M.R. Green, C.M. McCormick, Sex and stress steroids in adolescence: gonadal regulation of the hypothalamic–pituitary–adrenal axis in the rat, Gen. Comp. Endocrinol. 234 (2016) 110–116.
[49] F. Grodstein, J. Chen, D.A. Pollen, M.S. Albert, R.S. Wilson, M.F. Folstein, D.A. Evans, M.J. Stampfer, Postmenopausal hormone therapy and cognitive function in healthy older women, J. Am. Geriatr. Soc. 48 (2000) 746–752.
[50] C. Gurvich, K. Hoy, N. Thomas, J. Kulkarni, Sex differences and the influence of sex hormones on cognition through adulthood and the aging process, Brain Sci. 8 (2018).
[51] E. Hampson, Regulation of cognitive function by androgens and estrogens, Current Opinion in Behavioral Sciences 23 (2018) 49–57.
[52] D.K. Hamson, M.M. Roes, L.A. Galea, Sex hormones and cognition: neuroendocrine influences on memory and learning, Comp. Physiol. 6 (2016) 1295–1337.
[53] A.L. Heck, R.J. Handa, Sex differences in the hypothalamic-pituitary-adrenal axis' response to stress: an important role for gonadal hormones. Neuropsychopharmacology, official publication of the American College of Neuropsychopharmacology 44 (2019) 45–58.
[54] A. Herlitz, J.E. Yonker, Sex differences in episodic memory: the influence of intelligence, J. Clin. Exp. Neuropsychol. 24 (2002) 107–114.
[55] M. Hines, C. Brook, G.S. Conway, Androgen and psychosexual development: core gender identity, sexual orientation and recalled childhood gender role behavior in women and men with congenital adrenal hyperplasia (CAH), J. Sex. Res. 41 (2004) 75–81.
[56] R.M. Hoffman, L.D. Borders, Twenty-five years after the Bem Sex-Role Inventory: a reassessment and new issues regarding classification variability, Meas. Eval. Counsel. Dev. 34 (2001) 39–55.
[57] C.K. Hooven, C.F. Chabris, P.T. Ellison, S.M. Kosslyn, The relationship of male testosterone to components of mental rotation, Neuropsychologia 42 (2004) 782–790.
[58] J.T. Hua, K.L. Hildreth, V.S. Pelak, Effects of testosterone therapy on cognitive function in aging: a systematic review, Cognit. Behav. Neurol. 29 (2016) 122–138.
[59] J.S. Hyde, The gender similarities hypothesis, Am. Psychol. 60 (2005) 581–592.
[60] J.S. Hyde, Sex and cognition: gender and cognitive functions, Curr. Opin. Neurobiol. 38 (2016) 53–56.
[61] D.F. Janssen, Know thy gender: etymological primer, Arch. Sex. Behav. 47 (2018) 2149–2154.
[62] L.J. Julian, Measures of anxiety: state-trait anxiety inventory (stai), beck anxiety inventory (bai), and hospital anxiety and depression scale-anxiety (HADS-A), Arthritis Care Res. 11 (63) (2011) S467–S472.
[63] M.A. Karalexi, M.K. Georgakis, N.G. Dimitriou, T. Vichos, A. Katsimpris, E.T. Petridou, F.C. Papadopoulos, Gender-affirming hormone treatment and cognitive function in transgender young adults: a systematic review and meta-analysis, Psychoneuroendocrinology 119 (2020), 104721.
[64] S. Keyes, Sex-differences in cognitive-abilities and sex-role stereotypes in hong-kong Chinese adolescents, Sex. Roles 9 (1983) 853–870.
[65] D. Kimura, Sex differences in the brain, Sci. Am. 267 (1992) 118–125.
[66] S.M. Lamers, G.J. Westerhof, E.T. Bohlmeijer, P.M. ten Klooster, C.L. Keyes, Evaluating the psychometric properties of the mental health continuum-short form (MHC-SF), J. Clin. Psychol. 67 (2011) 99–110.
[67] J. Le, N. Thomas, C. Gurvich, Cognition, the menstrual cycle, and premenstrual disorders: a review, Brain Sci. 10 (2020).
[68] C. Lewin, G. Wolgers, A. Herlitz, Sex differences favoring women in verbal but not in visuospatial episodic memory, Neuropsychology 15 (2001) 165–173.
[69] R. Li, M. Singh, Sex differences in cognitive impairment and Alzheimer's disease, Front. Neuroendocrinol. 35 (2014) 385–403.

[70] H.M. Lips, Sandra Bem: naming the impact of gendered categories and identities, Sex. Roles 76 (2017) 627–632.
[71] S.J. Lupien, A. Fiocco, N. Wan, F. Maheu, C. Lord, T. Schramek, M.T. Tu, Stress hormones and human memory function across the lifespan, Psychoneuroendocrinology 30 (2005) 225–242.
[72] P.M. Maki, J.B. Rich, R.S. Rosenbaum, Implicit memory varies across the menstrual cycle: estrogen effects in young women, Neuropsychologia 40 (2002) 518–529.
[73] C. Maslach, S.E. Jackson, M.P. Leiter, W.B. Schaufeli, R.L. Schwab, Maslach burnout inventory, in: Consulting Psychologists Press, 3803 E. Bayshore Road, P.O. Box 10096, Palo Alto, CA, third ed., 1986.
[74] A.C. McCarrey, Y. An, M.H. Kitner-Triolo, L. Ferrucci, S.M. Resnick, Sex differences in cognitive trajectories in clinically normal older adults, Psychol. Aging 31 (2016) 166–175.
[75] M. Mitrushina, K.B. Boone, J. Razani, L.F. D'Elia, Handbook of Normative Data for Neuropsychological Assessment, Oxford University Press, 2005.
[76] K.L. Mordecai, L.H. Rubin, P.M. Maki, Effects of menstrual cycle phase and oral contraceptive use on verbal memory, Horm. Behav. 54 (2008) 286–293.
[77] S.C. Nash, Relationship among sex-role stereotyping, sex-role preference, and sex difference in spatial visualization, Sex. Roles 1 (1975) 15–32.
[78] S.C. Nash, Sex Role as a Mediator of Intellectual Functioning, in: M.A. Wittig, A.C. Peterson (Eds.), Academic Press, New York, 1979.
[79] R. Nass, S. Baker, Androgen effects on cognition: congenital adrenal hyperplasia, Psychoneuroendocrinology 16 (1991) 189–201.
[80] H.B. Nguyen, A.M. Chavez, E. Lipner, L. Hantsoo, S.L. Kornfield, R.D. Davies, C.N. Epperson, Gender-affirming hormone use in transgender individuals: impact on behavioral health and cognition, Curr. Psychiatr. Rep. 20 (2018) 110.
[81] B.M. Nugent, C.L. Wright, A.C. Shetty, G.E. Hodes, K.M. Lenz, A. Mahurkar, S.J. Russo, S.E. Devine, M.M. McCarthy, Brain feminization requires active repression of masculinization via DNA methylation, Nat. Neurosci. 18 (2015) 690–697.
[82] M. Numan, Chapter 4-Sexual Behaviors and Sexual Differentiation, Neurobiology of Social Behavior : toward an Understanding of the Prosocial and Antisocial Brain, Academic Press, 2015, pp. 109–164.
[83] A. Olsson, E. Kopsida, K. Sorjonen, I. Savic, Testosterone and estrogen impact social evaluations and vicarious emotions: a double-blind placebo-controlled study, Emotion 16 (2016) 515–523.
[84] D. Ostatníková, J. Hodosy, M. Skokňová, Z. Putz, M. Kúdela, P. Celec, Spatial abilities during the circalunar cycle in both sexes, Learn. Indiv Differ 20 (2010) 484–487.
[85] P.A. Osterrieth, Le test de copie d'une figure complexe; contribution à l'étude de la perception et de la mémoire. [Test of copying a complex figure; contribution to the study of perception and memory.], Arch. Psychol. 30 (1944) 206–356.
[86] M.G. Oyola, R.J. Handa, Hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes: sex differences in regulation of stress responsivity, Stress 20 (2017) 476–494.
[87] M.S. Panizzon, R.L. Hauger, H. Xian, K. Jacobson, M.J. Lyons, C.E. Franz, W.S. Kremen, Interactive effects of testosterone and cortisol on hippocampal volume and episodic memory in middle-aged men, Psychoneuroendocrinology 91 (2018) 115–122.
[88] C.W. Pintzka, H.R. Evensmoen, H. Lehn, A.K. Haberg, Changes in spatial cognition and brain activity after a single dose of testosterone in healthy women, Behav. Brain Res. 298 (2016) 78–90.
[89] B. Pletzer, T.A. Harris, T. Ortner, Sex and menstrual cycle influences on three aspects of attention, Physiol. Behav. 179 (2017) 384–390.
[90] S. Prasad, B. Lassetter, K.M. Welker, P.H. Mehta, Unstable correspondence between salivary testosterone measured with enzyme immunoassays and tandem mass spectrometry, Psychoneuroendocrinology 109 (2019).
[91] A.M. Proverbio, Sex differences in social cognition: the case of face processing, J. Neurosci. Res. 95 (2017) 222–234.
[92] J. Pryzgoda, J.C. Chrisler, Definitions of gender and sex: the subtleties of meaning, Sex. Roles 43 (2000) 553–569.
[93] D.A. Puts, R.A. Cárdenas, D.H. Bailey, R.P. Burriss, C.L. Jordan, S.M. Breedlove, Salivary testosterone does not predict mental rotation performance in men or women, Horm. Behav. 58 (2010) 282–289.
[94] D.A. Puts, M.A. McDaniel, C.L. Jordan, S.M. Breedlove, Spatial ability and prenatal androgens: meta-analyses of congenital adrenal hyperplasia and digit ratio (2D: 4D) studies, Arch. Sex. Behav. 37 (2008) 100–111.
[95] Q. Rahman, S. Abrahams, G.D. Wilson, Sexual-orientation-related differences in verbal fluency, Neuropsychology 17 (2003) 240–246.
[96] Q. Rahman, J. Sharp, M. McVeigh, M.L. Ho, Sexual orientation-related differences in virtual spatial navigation and spatial search strategies, Arch. Sex. Behav. 46 (2017) 1279–1294.
[97] Q. Rahman, G.D. Wilson, Large sexual-orientation-related differences in performance on mental rotation and judgment of line orientation tasks, Neuropsychology 17 (2003) 25–31.
[98] B.G. Reed, B.R. Carr, The normal menstrual cycle and the control of ovulation, in: K.R. Feingold, B. Anawalt, A. Boyce, et al. (Eds.), 2018. South Dartmouth (MA).
[99] D. Reilly, D.L. Neumann, G. Andrews, Sex and sex-role differences in specific cognitive abilities, Intelligence 54 (2016) 147–158.
[100] C. Rivier, S. Rivest, Effect of stress on the activity of the hypothalamic-pituitary-gonadal axis: peripheral and central mechanisms, Biol. Reprod. 45 (1991) 523–532.
[101] R.M. Ruff, R.H. Light, S.B. Parker, H.S. Levin, Benton controlled oral word association test: reliability and updated norms, Arch. Clin. Neuropsychol. 11 (1996) 329–338.
[102] A. Scheuringer, B. Pletzer, Sex differences and menstrual cycle dependent changes in cognitive strategies during spatial navigation and verbal fluency, Front. Psychol. 8 (2017) 381.
[103] S. Shepard, D. Metzler, Mental rotation: effects of dimensionality of objects and type of task, J. Exp. Psychol. Hum. Percept. Perform. 14 (1988) 3–11.
[104] R.P. Smith, R.M. Coward, J.R. Kovac, L.I. Lipshultz, The evidence for seasonal variations of testosterone in men, Maturitas 74 (2013) 208–212.
[105] R.S. Soleman, S.E.E. Schagen, D.J. Veltman, B.P.C. Kreukels, P.T. Cohen-Kettenis, C.B. Lambalk, F. Wouters, H.A. Delemarre-van de Waal, 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 (2013) 1969–1977.
[106] G. Stoet, D.C. Geary, Sex differences in mathematics and reading achievement are inversely related: within- and across-nation assessment of 10 years of PISA data, PloS One 8 (2013) e57988.
[107] D.F. Swaab, Sexual differentiation of the brain and behavior, Best Pract. Res. Clin. Endocrinol. Metabol. 21 (2007) 431–444.
[108] D.J. Swan, 2 models and measures of sexual orientation, in: D.J. Swan, S. Habibi (Eds.), Bisexuality: Theories, Research, and Recommendations for the Invisible Sexuality, Springer International Publishing, Cham, 2018, pp. 19–36.
[109] J. Taieb, B. Mathian, F. Millot, M.C. Patricot, E. Mathieu, N. Queyrel, I. Lacroix, C. Somma-Delpero, P. Boudou, Testosterone measured by 10 immunoassays and by isotope-dilution gas chromatography-mass spectrometry in sera from 116 men, women, and children, Clin. Chem. 49 (2003) 1381–1395.
[110] P.P. Thilers, S.W.S. MacDonald, A. Herlitz, The association between endogenous free testosterone and cognitive performance: a population-based study in 35 to 90 year-old men and women, Psychoneuroendocrinology 31 (2006) 565–576.
[111] J. Tiffin, E.J. Asher, The Purdue pegboard; norms and studies of reliability and validity, J. Appl. Psychol. 32 (1948) 234–247.
[112] T. Toivainen, G. Pannini, K.A. Papageorgiou, M. Malanchini, K. Rimfeld, N. Shakeshaft, Y. Kovas, Prenatal testosterone does not explain sex differences in spatial ability, Sci. Rep. 8 (2018) 13653.
[113] D. Tranel, E. Vianna, K. Manzel, H. Damasio, T. Grabowski, Neuroanatomical correlates of the Benton facial recognition test and judgment of line orientation test, J. Clin. Exp. Neuropsychol. 31 (2009) 219–233.
[114] L. Tucha, S. Aschenbrenner, J. Koerts, K.W. Lange, The five-point test: reliability, validity and normative data for children and adults, PloS One 7 (2012) e46080–e46080.
[115] A. Ulubaev, D.M. Lee, N. Purandare, N. Pendleton, F.C. Wu, Activational effects of sex hormones on cognition in men, Clin. Endocrinol. 71 (2009) 607–623.
[116] S.G. Vandenberg, A.R. Kuse, Mental rotations, a group test of three-dimensional spatial visualization, Percept. Mot. Skills 47 (1978) 599–604.
[117] D. Voyer, Time limits and gender differences on paper-and-pencil tests of mental rotation: a meta-analysis, Psychon. Bull. Rev. 18 (2011) 267–277.
[118] E. Vuoksimaa, J. Kaprio, C.J. Eriksson, R.J. Rose, Pubertal testosterone predicts mental rotation performance of young adult males, Psychoneuroendocrinology 37 (2012) 1791–1800.
[119] E.M. Weiss, J.D. Ragland, C.M. Brensinger, W.B. Bilker, E.A. Deisenhammer, M. Delazer, Sex differences in clustering and switching in verbal fluency tasks, J. Int. Neuropsychol. Soc. 12 (2006) 502–509.
[120] K.M. Welker, B. Lassetter, C.M. Brandes, S. Prasad, D.R. Koop, P.H. Mehta, A comparison of salivary testosterone measurement using immunoassays and tandem mass spectrometry, Psychoneuroendocrinology 71 (2016) 180–188.
[121] L. Wideman, M.M. Montgomery, B.J. Levine, B.D. Beynnon, S.J. Shultz, Accuracy of calendar-based methods for assigning menstrual cycle phase in women, Sport Health 5 (2013) 143–149.
[122] J.R. Wilson, J.C. Defries, G.E. Mcclearn, S.G. Vandenberg, R.C. Johnson, M.N. Rashad, Cognitive-abilities - use of family data as a control to assess sex and age-differences in 2 ethnic groups, Int. J. Aging Hum. Dev. 6 (1975) 261–276.
[123] S.P. Woods, D.C. Delis, J.C. Scott, J.H. Kramer, J.A. Holdnack, The California Verbal Learning Test - second edition: test-retest reliability, practice effects, and reliable change indices for the standard and alternate forms, Arch. Clin. Neuropsychol. 21 (2006) 413–420.
[124] Y. Xu, S. Norton, Q. Rahman, Sexual orientation and neurocognitive ability: a meta-analysis in men and women, Neurosci. Biobehav. Rev. 83 (2017) 691–696.
[125] Y. Xu, S. Norton, Q. Rahman, Sexual orientation and cognitive ability: a multivariate meta-analytic follow-up, Arch. Sex. Behav. 49 (2020) 413–420.
[126] G. Yararbas, S. Pogun, Activational effects of hormones, in: I.P. Stolerman (Ed.), Encyclopedia of Psychopharmacology, Springer Berlin Heidelberg, Berlin, Heidelberg, 2010, 15–15.
[127] R.F. Zec, M.A. Trivedi, The effects of estrogen replacement therapy on neuropsychological functioning in postmenopausal women with and without dementia: a critical and theoretical review, Neuropsychol. Rev. 12 (2002) 65–109.