Natalie Barthel, Dr. Tehmina Khwajah & Dr. Javeria Hashmi

Sex differences in pain sensitivity; biologically determined or psychosocial?

Women are suggested to be more pain sensitive than men across experimentally-induced and clinical pain tests (1-3). Several studies have highlighted important sex differences in animal pain behaviors that are biologically driven and are determined by genetics, immune mechanisms and hormones (4-6). Although the literature remains to be standardized, biological sex differences of pain exist that, indeed, contribute to the pain experience. However, in human studies, most sex differences in pain are limited to tests in measures of pain sensitivity and tolerance, the observed effect sizes are small, and the findings are variable across modalities and study context (7, 8). The trend is often in the direction of women demonstrating higher pain sensitivity than men. But, because evaluation and experience of pain are markedly influenced by social (11, 12) and developmental (2, 10, 13) factors as well as stereotypical gender roles (Walsh, Eccleston, & Keogh, 2017), there is an undeniable effect of these factors in human studies on sex differences. The affective and personality factors not only vary between the sexes, but are also a direct result of environmental and social stressors. Stress contributes to states of high vulnerability, hypervigilance to threats and fear of pain (14-17). Hence any sex differences in pain or in related psychosocial factors can affect men and women differently partly due to reproductive roles and to sociocultural roles and status. However, observed effects of sex differences in pain behavior in mice is often interpreted to represent biologically driven sex-differences in human pain behaviour (Mogil & Bailey, 2010; Mogil et al., 2011; Shaefer, J.R., Khawaja, & Bavia, 2018).

Pain research has yet to fully confront the complexity in human pain-related sex differences; hence, biology and psychosocial factors remain entangled in driving research on sex differences

in pain studies. Not only is the acknowledgement of psychosocial factors essential for the advancement of the science of sex differences in pain, but also for avoidance of inadvertent perpetuation of gender stereotypes. This review samples the influence of biological and psychological sex differences and their contribution to the perception of pain by men and women. Value is given to the neurobiological systems that influence and control pain perception through descending pathways that exert a top-down control on pain signals. Finally, this top-down processing system is placed within a sociocultural context in which people are influenced by social norms that negate or conflate expressing and feeling pain. The harms of biological determinism and exclusion of those on the gender spectrum outside of the binary categories of man/woman are discussed as a function of the sex-gender correlation and stereotyping.

We argue for a more comprehensive evaluation of inter-individual pain perception and treatment of chronic pain conditions.

What is pain sensitivity?

Defined by behavioural responses to pain, pain sensitivity is measured by pain threshold, pain tolerance and evoked responses. Pain modulatory processes have been defined by spatiotemporal dynamics of pain experience and are measured as temporal summation of pain, conditioned pain modulation (Fillingim, 2017), pain adaptation (Hashmi & Davis, 2008; 2009; & 2010), attention and expectation related pain modulation. Different modality tests for noxious pain include mechanical, electrical, thermal, ischaemic (Racine et al., 2012a,b; Ross et al., 2018), and chemical stimuli (Bartley & Fillingim, 2013); these tests are often assessed at different body sites with various pain and statistics measures (Racine et al., 2012a).

In relation to men, several studies claim to have found women to be the following: less tolerant of pain; reach threshold pain measures sooner; experience more discomfort and pain intensity; experience pain across more body sites; and have higher discrimination for pain stimuli (Berkley, 1997; Rollman et al., 2004; Keogh, 2006; Mogil, 2012; Berkley & Fillingim, 2013; Bulls et al., 2015; Fillingim, 2017). However, there is ample conflicting evidence for a 'true' sex difference within experimentally-induced pain research. The effect sizes are often marginal (Racine et al., 2012a,b) and the magnitude of the sex difference varies across pain modalities and studies, with inconsistent claims of evidence for a sex difference (Racine et al., 2012b). Indeed, there is evidence to suggest that some men and women show differences in their sensitivity to pain, but, overall, the data clearly show that most human populations show an overlap in their sensitivity to pain. Hence, not all women are more sensitive to pain than men, and not all men are more tolerant of pain than women; the within-sex variability has not been appropriately emphasized (Hashmi & Davis, 2014), and the concept of gender is often misconstrued.

Biological Sex vs. Socially Constructed Gender

Sex and gender are often not distinguished and even used interchangeably in pain research. Sex refers to the biological categorization of humans on the basis of chromosomes, hormones, and reproductive organs; gender, on the other hand, is a socially constructed classification of humans that relies on exaggerating differences between males and females (Padavic & Reskin, 2002). In evolutionary terms, the distinct reproductive roles of the sexes place a selection pressure towards differentiation between men and women. The sum result of this selection pressure is the differentiation of physical and psychosocial features that ensure reproduction and position women and men to identify with maternal and paternal roles, respectively, to ensure survival of

the human offspring. The sexual biology of humans and its impact on reproduction has been used as the justification for the division of labour, and control mechanisms of social behaviors and societal functions by gender (Lorber, 2005; Meade, & Wiesner-Hanks, 2004; Padavic & Reskin, 2002). Hence, traditionally, due to their disproportionately larger role in reproduction, women have been socialized to play a greater role in infant care than men (Meade, & Wiesner-Hanks, 2004). Moreover, due to the difference in average physical strength between the sexes, the responsibility to lead, protect and defend the clan has been claimed by men (van Vugt & Ahuja, 2011). Resultantly, social conventions exaggerate basic biological sex differences between men and women, and prescribe behaviours, traits, and labour suited to each of the two genders, while completely negating the concept of the gender spectrum or the existence of trans* or intersex individuals. This differentiation of the sexes along binary lines is the cornerstone of the social construction of gender, and the basis of social inequalities for women and those outside the gender binary (Butler, 2004).

Influence of Biology on Sex Differences in Pain Sensitivity

Research on sex differences in pain sensitivity demonstrates that nociceptive sensitivity can be influenced by genotype attributed to the female sex (Bartley & Fillingim, 2013). For example, as a result of the melanocortin-1 receptor gene mutation, red-haired women are more sensitive to thermal pain measures of hot and cold pain perception and tolerance (Liem et al., 2005). Young Han Chinese women with a single-nucleotide polymorphisms (SNPs) of the *NTRK1* gene, involved in sensory and sympathetic neuronal survival, have a reduction in pain sensitivity (Li et al., 2018). Women being both a carrier of a group of inherited genes, CTCC, and a carrier of one of four tag-SNPs have lower pain sensitivity to mechanically-induced pain (Li et al., 2018).

Thus, genetic differences, or lack thereof, may contribute to the variability of pain measures reported by women in the sex differences literature (Serdarevic, Striley & Cottler, 2017).

However, other biological explanations for sex differences in pain are more nuanced and require further deductive investigations. One such topic is difference in pain behavior related to hormones and is illustrated by early research in which transgender patients undergoing hormone replacement therapy had altered pain sensitivity (Aloisi et al., 2017). Thirty-three percent of male-to-female patients on testosterone blockers and estrogens developed painful conditions, such as musculoskeletal pain and headaches, whereas 62% of female-to-male patients reported improvement in previously diagnosed pain conditions (Aloisi et al., 2017). However, how the physical transition in these transgender patients contributed to this effect was not studied to describe the neurobiological changes occurring. Therefore, it cannot be concluded if these changes in pain sensitivity were driven by hormones alone. Indeed, testosterone has been suggested to have anti-nociceptive effects, whereas estrogen and progesterone have both been suggested to have indirect anti and pro-nociceptive effects (Bartley & Fillingim, 2013), but the effects of hormones on pain sensitivity are complex, having both pronociceptive or antinociceptive effects depending on experimental context (ref Zubieta 2006, Craft RM 20017).

Since the menstrual cycle is linked with changes in stress levels, affective state, anxiety and mood, any observation of pain or affect behavior co-varying with hormones can be deemed as biological (Marrocco & McEwen, 2016). But, in interpreting these effects, the confounding effects of differences in pain-related fear, environmental stressors and other contextual effects should not be ignored. Hence, to conclude that hormonal effects on pain sensitivity are purely biological is unwarranted until we observe more robust evidence to support such a position.

Influence of Top-Down Mental Processes on Pain Sensitivity

Although pain literature studies the experience of pain by assessing the bottom-up pain input pathway during external pain stimulation trials, the influence of top-down mental processes on the experience of pain must be discussed and included. The normative view of pain processing theorizes that bottom-up pain input are sent to the brain as peripheral signals (Bushnell et al., 2013). Neuronal signals transduced by nociceptors indeed ascend through pain pathways to higher brain centers to be interpreted as pain signals. Among the main functions of the ascending systems, a primary one is to detect physical threats, to identify their locus on the body and to generate quick responses in order to ensure survival. This, however, is not the only function of pain, since the experience is tied to both actual and potential threats. Ultimately, pain is a signal for adjusting behavior and a fundamental instinct to protect the body from physical harm and to ensure survival.

Pain pathways are unique in that nociceptive signals are regulated, controlled and modulated at several steps as the information ascends through the nerves and spinal cord to the brain. At each step, signals are processed and modulated through synaptic activity occurring in communicating structures that are interconnected through feedback loops. Information loops descending from supraspinal structures can both dampen nociceptive inputs or amplify them at the level of the spinal dorsal horn. The exact supraspinal systems and mental phenomenon that lead to these alterations are actively researched; there is ample evidence to suggest that contextual information processed in higher brain centers modify pain signals at the spinal level (citation). Whether these mechanisms operate differently between men and women because of differences because social context varies for men and women remains to be determined. For DNIC effect and conditioned pain modulation tests tested under controlled conditions, some

studies (Staud et al., 2003) have found differences (Frot, Feine, & Bushnell, 2004; Granot et al., 2008) while others reported no effect (France & Suchowiecki, 1999; Lautenbacher, Kunz, Burkhardt, 2008; Martel, Wasan, & Edwards, 2013).

A well-documented example of descending inhibition is aversive conditioning. It is a phenomenon in which prior learning is mediated through sub-cortical structures which modify associations between pain and noxious stimuli like objects or events (citation). These learned associations result in conditioned responses where innocuous stimuli significantly alter the experience of pain, previously evoked by the noxious event.

Another type of descending inhibition results from prior learning of context (citation). Contextual learning of high-order associations occurs in super-ordinate cognitive frameworks in the form of ideas, concepts and beliefs (citation). These contextual priors are believed to be processed in multimodal systems such as the frontal parietal networks, cingulo-opercular networks and reward centers (citation). These systems have been shown to modify pain perception through their interactions with specific brain stem regions (citation). In turn, the latter systems exert an influence on spinal processing of pain through descending pathways. The subjective and intransitive (word choice?) aspects of pain are unsurprising since context is learned through direct experience and the level of threat detected is individually specific. An event interpreted as a stronger threat evokes greater pain. Viewed from this vantage point, an important aspect of the pain system is threat *prediction* (i.e. perception) which complements its role in threat *detection* (i.e. sensation; Hashmi, 2018).

Need to add section on what is known about sex differences in pain modulation

Sociocultural Influences on Pain Perception – How is our perception of pain shaped?

Pain sensitivity literature clearly demonstrates a trend towards women being more sensitive to pain across modalities, but the high variability in findings is also indicative of contextual factors and that the observations are not purely biological (Mogil, 2012; Racine et al., 2012a).

Interdisciplinary scholars have argued that experiences of pain are not exclusively physiological, but consist of a complex web of psychosocial conditioning through social mores, religious edicts and even nationalist propaganda (Harari, 2015; Kahneman, 2011). Harari (2015), for example, questioned the very nature of the human experience of pain by postulating that the self that experiences is distinct from the self that narrates. This narrating self – a product of a person's sociocultural experiences and conditioning – takes over once the experience, including a physically painful one, ends (Harari, 2015). Hence, it is difficult to ascertain to what extent the experience of pain is purely physical or indeed biological rather than a complex psychosocial construct.

Consequently, sociocultural factors need to be taken into account when considering pain sensitivity. As noted earlier, threat prediction and detection are integral to pain processing in humans. In social contexts with clear social hierarchies based on gender and racial identity (Kim et al., 2017), individuals belonging to less privileged identity groups such as women, trans*, and racial minorities are more fearful of, and vulnerable to, threats such as physical, emotional and psychological violence than those belonging to privileged groups (Hollander, 2001; Scott, 2003). Hence, due to a more vulnerable position in social hierarchy, women and minorities experience added stress, which is known to increase cortisol levels (citation).

One useful illustration of vulnerability is the strong link between, fear of pain, anxiety (Moore, Eccleston, & Keogh, 2013) and pain sensitivity. Pain catastrophizing is a multi-dimensional construct comprised of rumination, helplessness, and pessimism; it is defined as a set of negative cognition and emotions associated to the belief that any experience with pain will result in worst outcomes (citation). Individuals' variability on this scale is a strong determinant of high pain sensitivity. Literature demonstrates a determinant effect of sex on pain catastrophizing, with the general consensus that females are more likely to catastrophize in response to pain than men (citation). Differences in pain catastrophizing were observed only in the rumination and helplessness subscale (citation). Whether this effect is reproducible is unclear and the exact mechanism responsible for these gender-based differences in pain catastrophizing are yet to be thoroughly explored. Furthermore, catastrophizing is linked with conditioned pain modulation (citation). However, social learning models have suggested that individuals who develop a pain-schema comorbidly catastrophize about pain (Straub et al., 2009). In line with social learning theory, it was found that young girls and boys are socialized differently to express pain responses (citation). Subsequently, this establishes the development of a catastrophic orientation to pain (citation).

Tehmina , can you make another point using the following material:

High vulnerability due to social/societal factors is putatively a factor for chronic pains,

Social vulnerability can also be a contributing factor to sex-differences in occurrence of chronic pain (Maurer et al., 2016). To illustrate, chronic pain sufferers share certain personality traits such as a tendency to exhibit high harm avoidance –characterized by fearfulness and sensitivity to criticism–and low self-directedness –low motivation and problems setting and maintaining recovery goals (Naylor et al., 2017). These traits are often associated with women

and racial minorities (Hollander, 2001; Massey, Charles, Lundy & Fischer, 2011; Scott, 2003). Furthermore, both catastrophizing pain (magnifying and ruminating) and diminished self-efficacy result in fearful avoidance of pain, rather than learning to cope and adapt to the pain experience (Bartley & Fillingim, 2013). This creates a vicious cycle of fear, pain avoidance, and continual suffering for socially vulnerable individuals (Bartley & Fillingim, 2013).

Tehimina: the connection between the last and subsequent points is missing, any help will be so useful.

In addition to the correlation between social vulnerability and the experience of pain, gender norms, although different cross-culturally (Nayak et al., 2000; Hobara, 2005; Alabas et al., 2013) prescribe gender-appropriate behaviour, including acceptable pain expression. Thus, for example, high masculinity scores are correlated with higher pressure pain thresholds and electrical pain tolerances (Alabas et al., 2012). Interestingly, high femininity scores are correlated with high pain sensitivity scores (Pool et al., 2007). This evidence of correlation between degree of masculinity or femininity and pain sensitivity is highly suggestive of the social construction of the gender binary characteristics associated with men/women such as strong/weak, protector/protected, fearless/fearful and so on (Connell, 2005; West & Zimmerman, 1987).

Indeed, patient-provider interaction studies demonstrate the internalization of binary gender roles. A study examining lay people's opinions of chronic low back pain (CLBP) patients found that endorsement of gender stereotypes correlated to perceiving men with CLBP as less masculine and more feminine, and women with CLBP as having lost their feminine role as affectionate caretakers (Bernandes & Lima, 2010). Interestingly, women and men with CLBP were perceived as more similar to one another, suggesting a tendency to diminish both genders

on the basis of their loss of traits typically associated with their gender (Bernandes & Lima, 2010). Furthermore, perception of the patient's gender results in altered assessment of pain; studies of gender priming found that participants with masculine primes perceived all patients as less distressed than participants with feminine primes (Pronina & Rule, 2014).

Human bodily experience evolves as a result of our development in society (Fausto-Sterling, 2000), which suggests that the experience of pain is highly complex and can develop alongside our gender identification. The differentiation of masculine and feminine traits guides conceptions of emotional vulnerability that influence perceived pain sensitivity according to gender roles, such as the willingness to report pain, which in turn, influences pain tolerance and intensity (Quiton & Greenspan, 2007; Racine et al., 2012b about Pool et al., 2007).

Recent studies are beginning to show a shift in gender roles in Western society (Gere & Helwig, 2012; Donnelly et al., 2015); more women are participating in sports that require pain resilience (Chalabaev et al., 2013) and pursue professions regardless of other commitments or health conditions (Gjerdingen et al., 2008). How these shifts are influencing the effects of psychosocial factors of pain perception and gender role on pain sensitivity remains to be explored. However, the gender binary appears to have substantial contribution to individual perception of pain.

Sex Differences or Gender Differences?

Unfortunately, sex is often not differentiated from gender in pain literature (Schiebinger & Stefanick, 2016; Clayton & Tannenbaum, 2016). This is problematic because not everyone relates to the gender identity socially ascribed to them based on their biological sex, and/or do not comply to the gender roles expected of them (Ferber et al., 2000; Clayton & Tannenbaum, 2016; NIH Office of Research on Women's Health, 2018). The degree to which an individual

conforms to or deviates from their assigned gender role can be considered to vary across a spectrum, as can the number of masculine or feminine traits that individuals endorse, manipulate, and/or transform (Ferber et al., 2000; Little, 2014; Clayton & Tannenbaum, 2016; NIH Office of Research on Women's Health, 2018). As such, there exists a spectrum of sex identity, a spectrum of gender identity, and a spectrum of gender expression; the possibility for combinations of characteristics between these spectra resemble the large variability across categories of gender (Keogh, Cheng & Wang, 2018) and sex (Butler, 2004; Lorber, 2005). These spectra for gender and sex have not been normalized within Western society and discourse, primarily composed of binary systemic structures (Ferber et al., 2000; Clayton & Tannenbaum, 2016).

Because gender binary beliefs are societally established as norms, this structure perpetuates stereotypes that an individual's gender defines their role in society (Little, 2014; Padavic & Reskin, 2002). The implications for this are problematic as stereotypes restrict access to career and/or social opportunities for people who are considered to not 'fit' the societal norm. With respect to (intersectional) feminist theory (Davis, 2008; Van Herk, Smith, & Andrew, 2011) in career opportunities, this is the division between individuals who are privileged due to identities (white, cisgender male, upper-class, able-bodied, educated, etc.) that are defined as advantageous workers versus oppressed identities (i.e. people of colour, women, disabled, impoverished, uneducated, etc.). This preference is evident within the world of STEM (science, technology, engineering, mathematics) disciplines, exemplified by James Damore and his Google memo, wherein women are believed to be inherently incapable of working within this sector (Marsh & Scalas, 2011; Ertl, Luttenberger, & Paechter, 2017). The privilege that white, cisgender men enjoy in western cultures creates advantages that are closed to anyone falling outside this

particular identity group (Wratten, Eccleston, & Keogh, 2019). When dealing with questions of pain, the confounding effect of privilege based on gender and race cannot be discounted.

Thus, stereotypical gender binaries unfairly limit access to career opportunities and maintain limits to what women (and other oppressed identities) can be expected to socially, financially, physically, emotionally, psychologically and cognitively achieve (Davis, 2008; Ferber et al., 2000; Little, 2014). Additionally, the perception of being vulnerable owing to gender and race compounds the emotional toll a given situation may take on an individual – including their perception of real or imagined pain or threat of pain.

Conclusion

This review supports the conclusion that biological, psychological and sociocultural factors have a respectably large contribution to the construction of pain experience. The authors support previous research claiming that pain is not a hardwired response system and is, instead, a complicated network of threat perception and assessment with respect to learned behaviour (Bushnell et al., 1985; Hashmi & Davis, 2014; Melchior et al., 2016; Hashmi, 2018). Conformity to gender roles is suggested to contribute to shaping pain perception and experience, and sex differences cannot be isolated amongst the plethora of intersecting identities that contribute to individual pain experience.

References

Alabas, O. A., Tashani, O. A., & Johnson, M. I. (2013). Effects of ethnicity and gender role expectations of pain on experimental pain- A cross-cultural study. *European Journal of Pain*, *17*, 776-786. https://doi.org/10.1002/j.1532-2149.2012.00229.x

Aloisi, A. M., Bachiocco, V., Costantino, A., Stefani, R., Ceccarelli, I., Bertaccini, A., & Meriggiola, M. C. (2007). Cross-sex hormone administration changes pain in transsexual women and men. *Pain*, *132*, S60-S67. https://doi.org/10.1016/j.pain.2007.02.006

Bagby, R.M., Widiger, T.A. (2018). Five-Factor Model (FFM) personality disorder scales: An introduction to a special section on assessment of maladaptive variants of the FFM. *Psychological Assessment, 30*(1), 1-9. https://doi.org/10.1037/pas0000523

Bartley, E. J., & Fillingim, R. B. (2013). Sex differences in pain: A brief review of clinical and experimental findings. *British Journal of Anaesthesia*, *111*(1), 52-58. https://doi.org/10.1093/bja/aet127

Bartley, E. J., Robinson, M. E., & Staud, R. (2017). Pain and fatigue variability patterns distinguish subgroups of fibromyalgia patients. *The Journal of Pain*.

Berkley, K. J. (1997). Sex differences in pain. *Behavioral and Brain Sciences, 20*(3), 371-380.

Bernardes, S. F., & Lima, M. L. (2010). Being less of a man or less of a woman: Perceptions of chronic pain patients' gender identities. *European Journal of Pain*, *14*, 194-199. https://doi.org/10.1016/j.ejpain.2009.04.009

Block, P., Heathcote, L. C., & Heyes, S. B. (2018). Social interaction and pain: An arctic expedition. *Social Science & Medicine*, *196*, 47-55. https://doi.org/10.1016/j.socscimed.2017.10.028

Brickhouse, N. W., Lowery, P., Schultz, K. (1999). What kind of a girl does science? The construction of school science identities. *JRST, 37*(5), 441-458.

Bulls, H. W., Freeman, E. L., Anderson, A. J. B., Robbins, M. T., Ness, T. J., & Goodin, B. R. (2015). Sex differences in experimental measures of pain sensitivity and endogenous pain inhibition. *Journal of Pain Research, 8*, 311-320. https://doi.org/10.2147/JPR.S84607

Bushnell, M. C., Duncan, G. H., Dubner, R., Jones, R. L., Maixner, W. (1985). Attentional influences on noxious and innocuous cutaneous heat detection in humans and monkeys. *J Neurosci, 5*(5), 1103-1110.

Bushnell, M. C., Čeko, M., Low, L. A. (2013). Cognitive and emotional control of pain and its disruption in chronic pain. *Nat Rev Neurosci, 14*(7), 502-511. https://doi.org/10.1038/nrn3516

Butler, J. (2004) *Undoing gender*. New York, NY: Routledge.

Chalabaev, A., Sarrazin, P., Fontayne, P., Boiché, J., Clémemnt-Guillotin, C. (2013). The influence of sex stereotypes and gender roles on participation and performance in sport and exercise: Review and future directions. *Psychol Sport Exerc, 14*(2), 136-144. https://doi.org/10.1016/j.psychsport.2012.10.005

Clayton, J. A., Tannenbaum, C. (2016). Reporting sex, gender, or both in clinical research? *JAMA, 316*(18), 1863-64. https://doi.org/10.1001/jama.2016.16405

Conger, K. (2017, August 8). Exclusive: Here's the full 10-page anti-diversity screed circulating internally at Google [Updated]. Retrieved March 6, 2018, from Gizmodo website: https://gizmodo.com/exclusive-heres-the-full-10-page-anti-diversity-screed-1797564320

Connell, R. (2005). *Masculinities.* Los Angeles, CA: University of California Press.

Davis, K. (2008). Intersectionality as buzzword: A sociology of science perspective on what makes a feminist theory successful. *Feminist Theory, 9*(1).

https://doi.org/10.1177/1464700108086364

Donnelly, K., Twenge, J.M., Clark, M.A., Shaikh, S.K., Beiler-May, A., Carter, N.T. (2015). Attitudes toward women's work and family roles in the United States, 1976-2013. *Psychol Women Q, 40*(1), 41-54. https://doi.org/10.1177/0361684315590774

Ertl, B., Luttenberger, S., & Paechter, M. (2017). The impact of gender stereotypes on the self-concept of female students in STEM subjects with an under-representation of females. *Front Psychol, 8*(703), 1-11. https://doi.org.10.3389/fpsych.2017.00703

Ferber, A. L., Holcomb, K., & Wentling, T. (2000). Dualing dualisms. In A. Fausto-Sterling (Author), *Sexing the body: Gender politics and the construction of sexuality*. Basic Books. (Reprinted from *The New Basics: Sex, gender, and sexuality*, 2nd ed., pp. 6-48, 2013, New York, NY: Oxford University Press)

Fillingim, R. J. (2017). Individual differences in pain: Understanding the mosaic that makes pain personal. *Pain, 158*(4), S11-S18. http://dx.doi.org/10.1097/j.pain.0000000000000775

France, C.R., Suchowiecki, S. (1999). A comparison of diffuse noxious inhibitory controls in men and women. *Pain, 81*(1-2), 77-84. https://doi.org/10.1016/S0304-3959(98)00272-3

Frot, M., Jocelyne, F., Bushnell, C.M. (2004). Sex differences in pain perception and anxiety: A psychophysical study with tocial capsaicin. *Pain, 108*(3), 230-236. https://doi.org/10.1016/j.pain.2003.11.017

Gatchel, R. J., Peng, Y. B., Peters, M. L., Fuchs, P. N., & Turk, D. C. (2007). The biopsychosocial approach to chronic pain: Scientific advances and future directions. *Psychological Bulletin, 133*(4), 581-624. https://doi.org/10.1037/0033-2909.133.4.581

Gere, J., Helwig, C.C. (2012). Young adults' attitudes and reasoning about gender roles in the family context. *Psychol Women Q, 36*(3), 301-313.

https://doi.org/10.1177/0361684312444272

Gjerdingen, D., McGovern, P., Bekker, M., Lundberg, U., Willemsen, T. (2008). Women's work roles and their impact on health, well-being, and career: Comparisons between the United States, Sweden, and the Netherlands. *Women & Health*, *31*(4), 1-20. https://doi.org/10.1300/J013v31n04_01

Glajchen, M. (2011). Chronic pain: Treatment barriers and strategies for clinical practice. *Journal of American Board of Family Practice*, *14*, 211-218.

Granot, M., Weissman-Fogel, I., Crispel, Y., Pud, D., GRanovsky, Y., SPrecher, E., Yarnistky, D. (2008). Determinants of endogenous analgesia magnitude in a duffuse noxious inhibitory control (DNIC) paradigm: Do conditioning stimulus painfulness, gender, and personality variables matter? *Pain*, *136(*1-2), 142-149. https://doi.org/10.1016/j.pain.2007.06.029

Harari, Y. N. (2016). *Homo Deus: A brief history of tomorrow*. United Kingdom: Random House.

Hashmi, J.A., Davis, K.D. (2008). Effect of static and dynamic heat pain stimulus profiles on the temporal dynamics and interdependence of pain qualities, intensity, and affect. *J Neuro Phys*, *100*(4), 1706-1715. https://doi.org/10.1152/jn.90500.2008

Hashmi, J.A., Davis, K.D. (2009). Women experience greater heat pain adaptation and habituation than men. *Pain*, *145*(3), 350-357. https://doi.org/10.1016/j.pain.2009.07.002

Hashmi, J.A., Davis, K.D. (2010). Effects of temperature on heat pain adaptation and habituation in men and women. *Pain*, *151*(3), 737-743. https://doi.org/10.1016/j.pain.2010.08.046

Hashmi, J.A., Baliki, M.N., Huang, L., Baria, A.T., Torbey, S., Hermann, K.M., … Apkarian, A.V. (2013). Shape shifting pain: Chronification of back pain shifts brain representation from

nociceptive to emotional circuits. *Brain J Neurol*, *136*, 2751-2768. https://doi.org/10.1093/brain/awt211

Hashmi, J.A., Davis, K.D. (2014). Deconstructing sex differences in pain sensitivity. *Pain, 155*, 10-13. https://doi.org/10.1016/j.pain.2013.07.039

Hashmi, J.A., Kong, J., Spaeth, R., Khan, S., Kaptchuk, T.J., Gollub, R.L. (2014). Functional network architecture predicts psychologically mediated analgesia related to treatment in chronic knee pain patients. *J Neurosci*, *34*(11), 3924-3936. https://doi.org/10.1523/jneurosci.3155-13.2014

Hashmi, J. (2018). Chapter 21: Placebo effect: Theory, mechanisms and teleological roots. In L. Colloca (Ed.), *Neurobiology of the Placebo Effect Part II* (Vol. 138). Elsevier.

Hernandez-Leon, A., De la Luz-Cuellar, Y. E., Granados-Soto, V., González-Trujano, M. E., & Fernández-Guasti, A. (2016). Sex differences and estradiol involvement in hyperalgesia and allodynia in an experimental model of fibromyalgia. *Hormones and Behaviour*, *97*, 39-46.

Hirsh, A. T., Hollingshead, N. A., Matthias, M. S., Bair, M. J., & Kroenke, K. (2014). The influence of patient sex, provider sex, and sexist attitudes on pain treatment decisions. *The Journal of Pain*, *15*(5), 551-559. http://dx.doi.org/10.1016/j.jpain.2014.02.003

Hobara, M. (2005). Beliefs about appropriate pain behavior: Cross-cultural and sex differences between Japanese and Euro-Americans. *European Journal of Pain*, *9*, 389-393. https://doi.org/10.1016/j.ejpain.2004.09.006

Hollander, J. A. (2001). Vulnerability and dangerousness: The construction of gender through conversation about violence. *Gender & Society*, *15*(1), 83-109.

Kahneman, D. (2011). *Thinking fast and slow*. New York, NY: Farrar, Straus & Giroux.

Keogh, E. (2006). Sex and gender differences in pain: A selective review of biological and

psychosocial factors. *Journal of Men's Health & Gender, 3*(3), 236-243. https://doi.org/10.1016/j.jmhg.2006.03.006

Keogh, E., Cheng, F., Wang, S. (2018). Exploring attentional biases towards facial expressions of pain in men and women. *Eur J Pain, 22*(9), 1617-1627. https://doi.org/10.1002/ejp.1244

Kim, H.J., Yang, G.S., Greenspan, J.D., Downton, K.D., Griffith, K.A., Renn, … Dorsey, S.G. (2017). Racial and ethnic differences in experimental pain sensitivity: Systemic review and meta-analysis. *Pain, 158*(2), 194-211. https://doi.org/10.1097/j.pain.0000000000000731

Langford, D.J., Tuttle, A.H., Brown, K., Deschenes, S., Fischer, D.B. Mutso, A., … Sternberg, W.F. (2010). Social approach to pain in laboratory mice. *Social Neuroscience, 5*(2), 163-170. https://doi.org/10.1080/17470910903216609

Lautenbacher, S., Kunz, M., Burkhardt, S. (2008). The effects of DNIC-type inhibition on temporal summation compared to single pulse processing: Does sex matter? *Pain, 140*(3), 429-435. https://doi.org/10.1016/j.pain.2008.09.019

Lee, T. B. (2018, January 9). Google fired James Damore for a controversial gender memo--now he's suing. Retrieved March 6, 2018, from arstechnica website: https://arstechnica.com/tech-policy/2018/01/lawsuit-goes-after-alleged-anti-conservative-bias-at-google/

Liedl, A., Knaevelsrud, C. (2008). Chronic pain and PTSD: The perpetual avoidance model and its treatment implications. *Torture 18*(2), 69-76.

Liem, E. B., Joiner, T. V., Tsued, K., Sessler, D. I. (2005). Increased sensitivity to thermal pain and reduced subcutaneous lidocaine efficacy in redheads. *Anesthesiology, 102*(3), 509-514.

Little, W. (2014). Gender, sex, and sexuality. In W. Little, S. Vyain, G. Scaramuzzo, S. Cody-Rydzewski, H. Griffiths, E. Strayer, . . . R. McGivern (Authors), *Introduction to*

Sociology: 1st Canadian edition.

Lorber, J. (2005). *Gender inequality.* Los Angeles, CA: Roxbury Publishing Company.

Maj, J. (2013). The significance of intersectionality for feminist political theory. *E-International Relations Students*, University of Manchester.

Marrocco, J. McEwen, B.S. (2016). Sex in the brain: Hormones and sex differences. *Dialogues CLin Neurosci, 18*(4), 3730383. https://doi.org/10.1016/S0065-2660(07)59009-7

Martel, M.O., Wasan, A. D., Edwards, R.R. (2013). Sex differences in the stability of conditioned pain modulation (CPM) among patients with chronic pain. *Pain Med, 14*(11), 1757-1768. https://doi.org/10.1111/pme.12220

Massey, D. S., Charles, C. Z., Lundy, G., & Fischer, M. J. (2011). *The source of the river: The social origins of freshmen at America's selective colleges and universities* (Vol. 61). Princeton, NJ: Princeton University Press.

Maté, G., M.D. (2004). *When the body says no: The cost of hidden stress*.

Mauer, A.J., Lissounov, A., Knezevic, I., Candido, K.D., Knezevic, N.N. (2016). Pain and sex hormones: A review of current understanding. *Pain Manag, 6*(3), 285-296. https://doi.org/10.2217/pmt-2015-0002

May, C., Brcic, V., Lau, B. (2018). Characteristics and complexity of chronic pain patients referred to a community-based multidisciplinary chronic pain clinic. *Can J Pain, 2*(1), 125-134. https://doi.org/10.1080/24740527.2018.1453751

Meade, T. A., & Wiesner-Hanks, M. E. (Eds.). (2004). *A companion to gender history*. Malden, MA: Blackwell Publishing Ltd.

Melchior, M., Poisbeau, P., Gaumond, I., Marchand, S. (2016). Insights into the mechanisms and the emergence of sex-differences in pain. *Neurosci, 338,* 63-80. https://doi.org/10.1016/j.neuroscience.2016.05.007

Messerschmidt, J. W. (2013). Goodbye to the sex-gender distinction, hello to embodied gender: On masculinities, bodies, and violence. In A. L. Ferber, K. Holcomb, & T. Wentling (Authors), *The New Basics: Sex, gender, and sexuality* (2nd ed.). New York, NY: Oxford University Press.

Mogil, J.S., Wilson, S.G., Chesler, E.J., Rankin, A.L., Nemmani, K.V., Lariviere, W.R., … & Fillingim, R.B. (2003). The melanocortin-1 receptor gene mediates female-specific mechanisms of analgesia in mice and humans. *Proc Natl Acad Sci USA, 100*(8), 4867-4872. https://doi.org/10.1073/pnsa.0730053100

Mogil, J. S., Sorge, R. E., LaCroix-Fralish, M. L., Smith, S. B., Fortin, A., Sotocinal, S. G., … & Fillingim, R. B. (2011). Pain sensitivity and vasopressin analgesia are mediated by a gene-sex-environment interaction. *Nature Neuroscience*, *14*, 1569-1573. https://doi.org/10.1038/nn.2941

Mogil, J. S. (2012). Sex differences in pain and pain inhibition- multiple explanations of a controversial phenomenon. *Nature Reviews, 13*, 859-866.

Moore, D.J., Eccleston, C., Keogh, E. (2013). Does sex moderate the relationship between anxiety and pain? *Psychol Health, 28*(7), 746-764. https://doi.org/10.1080/08870446.2012.759222

Mulak, A., Taché, Y., & Larauche, M. (2014). Sex hormones in the modulation of irritable bowel syndrome. *World Journal of Gastroenterology, 20*(10), 2433-2448. https://doi.org/10.3748/wjg.v20.i10.2433

Nayak, S., Shiflett, S. C., Eshun, S., & Levine, F. M. (2000). Culture and gender effects in pain beliefs and the prediction of pain tolerance. *Cross-Cultural Research, 34*(2), 135-151.

Naylor, B., Boag, S., Gustin, S.M. (2017). New evidence for a pain personality? A critical review of the last 120 years of pain and personality. *Scandinavian Journal of Pain*, *17*:58-67. https://doi.org/10.1016/j.sjpain.2017.07.011

NIH Office of Research on Women's Health. http://orwh.od.nih.gov/research/sex-gender. Accessed August 2, 2018.

Quinton, R.L., Greenspan, J.D. (2007). Sex differences in endogenous pain modulation by distracting and painful conditioning stimulation. *Pain, 132*(S1), 134-149. https://doi.org/10.1016/j.pain.2007.09.001

Padavic, I., & Reskin, B. (2002). *Men and women at work.* Thousand Oaks, CA: Pine Forge Press.

Pool, G.J., Schwegler, A.F., Theodore, B.R., Fuchs, P.N. (2007). Role of gender norms and group identification on hypothetical and experimental pain tolerance. *Pain, 129*(1-2), 122-129. https://doi.org/10.1016/j.pain.2006.10.008

Pronina, I., & Rule, N. O. (2014). Inducing bias modulates sensitivity to nonverbal cues of others' pain. *European Journal of Pain, 18*, 1452-1457. https://doi.org/10.1002/ejp.510

Racine, M., Tousignant-Laflamme, Y., Kloda, L.A., Dion, D., Dupuis, G., Choinière, M. (2012a). A systematic literature review of 10 years of research on sex/gender and experimental pain perception – Part 1: Are there really differences between women and men? *Pain, 153*, 602-618. https://doi.org/10.1016/j.pain.2011.11.025

Racine, M., Tousignant-Laflamme, Y., Kloda, L.A., Dion, D., Dupuis, G., Choinière, M. (2012b). A systematic literature review of 10 years of research on sex/gender and

experimental pain perception – Part 2: Do biopsychosocial factors alter pain sensitivity differently in women and men? *Pain, 153,* 619-635. https://doi.org/10.1016/j.pain.2011.11.026

Ramírez-Maestre, C., & Esteve, R. (2014). The role of sex/gender in the experience of pain: Resilience, fear, and acceptance as central variables in the adjustment of men and women with chronic pain. *The Journal of Pain*, *15*(6), 608-618. https://doi.org/10.1016/j.j.pain.2014.02.006

Rhudy, J.L., Williams, A.E. (2005). Gender differences in pain: Do emotions play a role? *Gend Med*, *2*(4), 208-226. https://doi.org/10.1016/S1550-8579(05)80051-8

Richards, R. J. (1974). The innate and the learned: The evolution of Konrad Lorenz's theory of instinct. *Philosophy of Social Science*, *4*, 111-133.

Rolke, R., Baron, R., Maier, C., Tölle, T.R., Treede, R.-D., Beyer, A., … Wasserka, B. (2006). Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values. *Pain, 123*(3), 231-243. https://doi.org/10.1016/j.pain.2006.01.041

Rollman, G. B., Abdel-Shaheed, J., Gillespie, J. M., & Jones, K. S. (2004). Does past pain influence current pain: Biological and psychosocial models of sex differences. *Pain, 8,* 427-433. https:://doi.org/10.1016/j.ejpain.2004.03.002

Scheim, A. I., Bauer, G. R. (2015). Sex and gender diversity among transgender persons in Ontario, Canada: Results from a respondent-driven sampling survey. *J Sex Research, 51*(1), 1-14. https://doi.ort/10.1080/00224499.2014.893553

Schertzinger, M., Wesson-Sides, K., Parkitny, L., & Younger, J. (2017). Daily fluctuations of progesterone and testosterone are associated with fibromyalgia pain severity. *The Journal of*

Pain, 1-8. https://doi.org/10.1016/j.jpain.2017.11.013

Schiebinger, L., Stefanick, M. L. (2016). Gender matters in biological research and medical practice. *AM J Coll Cardiol, 67*(2), 136-8. https://doi.org/10.1016/j.jacc.2015.11.029

Scott, H. (2003). Stranger danger: Explaining women's fear of crime. *Western Criminology Review, 4*(3): 203-214.

Serdarevic, M., Striley, C.W., Cottler, L.B. (2017). Sex differences in prescription opioid use. *Curr Op Psych, 30*(4), 238-246. https://doi.org/10.1097/YCO.0000000000000337

Shaefer, J.R., Khawaja, S.N., Bavia, P.F. (2018). Sex, gender, and orofacial pain. *Dent Clin North Am, 62*(4), 665-682. https://doi.org/10.1016/j.cden.2018.06.001

Siegling, A.B., Furnham, A., Petride, K.V. (2015). Trait emotional intelligence and personality: Gender-invariant linkages across different measures of the big five. *Journal of Psychoeducational Assessment, 33*(1):57-67. https://doi.org/10.1177/07342829

Sociobiology Study Group of Science for the People. (1976). Sociobiology: Another biological determinism. *BioScience, 26*(3), 182-186. http://www.jstor.org/stable/1297246

Straub, T., Schmidt, S., Weiss, T., Mentzel, H.J., Miltner, W.H. (2009). Sex differences in brain activation to anticipated and experienced pain in themedial prefrontal cortex. *Hum Brain Mapp, 30*(2), 689-698. https://doi.org/10.1002/hb.20536

Staud, R., Robinson, M.E., Vierck, C.J. Jr., Price, D.D. (2003). DIffuse noxious inhibitory controls (DNIC) attenuate temporal summation of second pain in normal males but not in normal females or fibromyalgia patients. *Pain, 101*(1-2), 167-174. https://doi.org/10.1016/S0304-3959(02)00325-1

Sullivan, M.J.L., Tripp, D.A., Santor, D. (2000). Gender differences in pain and pain behavior: The role of catastrophizing. *Cognitive Therapy and Research, 24*(1), 121-134.

https://doi.org/10.1023/A:1005459110063

Thorn, B.E., Clements, K.L., Ward, L.C., Dixon, K.E., Kersh, B.C., Boothby, J.L., Chaplin, W.F. (2004). Personality factors in the explanation of sex differences in pain catastrophizing and response to experimental pain. *Clinical Journal of Pain*, *20*(5), 275-282. https://doi.org/10.1097/00002509-200409000-00001

Van Herk, K. A., Smith, D., Andrew, C. (2011). Examining our privileges and oppressions: Incorporating an intersectional paradigm into nursing. *Nursing Inquiry*, *18*(1), https://doi.org/10.1111/j.1440-1800.2011.00539.x

van Vugt, M., & Ahuja, A. (2011). *Naturally selected: The evolutionary science of leadership.* New York, NY: HarperCollins.

Vlaeyen, J. W. S., Linton, S. J. (2000). Fear-avoidance and its consequences in chronic musculoskeletal pain: A state of the art. *Pain*, *85*, 317-332.

Walsh, J., Eccleston, C., Keogh, E. (2017). Sex differences in the decoding of pain-related body postures. *European Journal of Pain*, *21*, 1668-1677. https://doi.org/10.1002/ejp.1072

West, C., & Zimmerman, D. H. (1987). Doing gender. *Gender and Society*, *1*(2), 125-151.

White, H. D., & Robinson, T. D. (2015). A novel use for testosterone to treat central sensitization of chronic pain in fibromyalgia patients. *International Immunopharmacology*, *27*, 244-248. http://dx.doi.org/10.1016/j.intimp.2015.05.020

Wratten, S., Eccleston, C., Keogh, E. (2019). Perceptions of gendered and ungendered pain relief norms and stereotypes using Q-methodology. *Pain*, *160*(2), 395-406. https://doi.org/10.1097/j.pain.0000000000001409

Wong, J. C. (2017, August 8). Google reportedly fires author of anti-diversity memo. Retrieved March 6, 2018, from The Guardian website:

https://www.theguardian.com/technology/2017/aug/08/google-fires-author-anti-diversity-memo

1. Mogil JS & Bailey AL (2010) Sex and gender differences in pain and analgesia. *Progress in brain research* 186:141-157.
2. Greenspan JD*, et al.* (2007) Studying sex and gender differences in pain and analgesia: a consensus report. *Pain* 132 Suppl 1:S26-45.
3. Lasselin J, Lekander M, Axelsson J, & Karshikoff B (2018) Sex differences in how inflammation affects behavior: What we can learn from experimental inflammatory models in humans. *Front Neuroendocrinol* 50:91-106.
4. McEwen BS & Milner TA (2017) Understanding the broad influence of sex hormones and sex differences in the brain. *J Neurosci Res* 95(1-2):24-39.
5. Sorge RE & Totsch SK (2017) Sex Differences in Pain. *J Neurosci Res* 95(6):1271-1281.
6. Mogil JS (2012) Sex differences in pain and pain inhibition: multiple explanations of a controversial phenomenon. *Nat Rev Neurosci* 13(12):859-866.
7. Racine M*, et al.* (2012) A systematic literature review of 10 years of research on sex/gender and pain perception - part 2: do biopsychosocial factors alter pain sensitivity differently in women and men? *Pain* 153(3):619-635.
8. Racine M*, et al.* (2012) A systematic literature review of 10 years of research on sex/gender and experimental pain perception - part 1: are there really differences between women and men? *Pain* 153(3):602-618.
9. Meints SM, Wang V, & Edwards RR (2018) Sex and Race Differences in Pain Sensitization among Patients with Chronic Low Back Pain. *J Pain*.
10. Melchior M, Poisbeau P, Gaumond I, & Marchand S (2016) Insights into the mechanisms and the emergence of sex-differences in pain. *Neuroscience* 338:63-80.
11. Bartley EJ & Fillingim RB (2013) Sex differences in pain: a brief review of clinical and experimental findings. *British journal of anaesthesia* 111(1):52-58.
12. Ahn H, Weaver M, Lyon D, Choi E, & Fillingim RB (2017) Depression and Pain in Asian and White Americans With Knee Osteoarthritis. *J Pain* 18(10):1229-1236.
13. Prusator DK & Greenwood-Van Meerveld B (2016) Sex-related differences in pain behaviors following three early life stress paradigms. *Biology of sex differences* 7:29.
14. Borsbo B, Gerdle B, & Peolsson M (2010) Impact of the interaction between self-efficacy, symptoms and catastrophising on disability, quality of life and health in with chronic pain patients. *Disability and rehabilitation* 32(17):1387-1396.
15. Meulders A, Jans A, & Vlaeyen JWS (2015) Differences in pain-related fear acquisition and generalization: an experimental study comparing patients with fibromyalgia and healthy controls. *PAIN* 156(1):108-122.
16. Horn ME, Alappattu MJ, Gay CW, & Bishop M (2014) Fear of severe pain mediates sex differences in pain sensitivity responses to thermal stimuli. *Pain Res Treat* 2014:897953.

17. Peters ML, Vlaeyen JW, & Kunnen AM (2002) Is pain-related fear a predictor of somatosensory hypervigilance in chronic low back pain patients? *Behaviour research and therapy* 40(1):85-103.
18. Moore DJ, Eccleston C, & Keogh E (2013) Does sex moderate the relationship between anxiety and pain? *Psychol Health* 28(7):746-764.
19. Robinson ME, Wise EA, Gagnon C, Fillingim RB, & Price DD (2004) Influences of gender role and anxiety on sex differences in temporal summation of pain. *J Pain* 5(2):77-82.