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Variability in Symptom Reporting: The Effect of Menstrual Cycle Phase on Post-Concussive Symptom Reporting in Non-Concussed Adults

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By

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ABSTRACT

OBJECTIVES: Many symptoms associated with concussion are also associated with symptoms related the menstrual cycle, for example headache, nausea, and fatigue. This study sought to investigate the relationship between these symptoms at different points in the menstrual cycle to determine if it is appropriate to compare baseline symptom reports obtained in one menstrual phase with post-concussive symptom reports from another.

METHODS: 17 female and 11 male participants recruited from the psychology participant pool were given a measure of post-concussive symptoms (PCSS) and a measure of mood and stress symptoms (DASS). Females were also given a menstrual symptom questionnaire (DSRS). Participants completed the questionnaires on two occasions, two weeks apart. Females completed the questionnaires once during the follicular phase of their menstrual cycle and once during the luteal phase.

RESULTS: No significant differences between female and male reports on the PCSS or DASS were found. Symptoms on the DASS were found to decrease over time. PCSS and DSRS scores in females were significantly correlated at both time points, but more strongly correlated during the luteal phase. PCSS scores over time were correlated in male but not female participants.

CONCLUSIONS: The absence of significant results indicating an increase in the number and severity of symptoms experienced by females during the luteal phase suggests that there may be no need to control for menstrual phase at baseline. However, given that female PCSS scores were not correlated between times 1 and 2, type of symptoms may vary even if overall number and severity do not.

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CHAPTER 1

RELEVANCE AND IMPORTANCE

Mild traumatic brain injuries (mTBI) have been identified as an important health problem deserving of more attention in order to prevent the incidence of new injuries (Upshur & Echlin, 2014). In the context of sports injuries, mTBIs are commonly referred to as concussions and generally represent mTBIs of mild severity. The incidence of sports-related concussion is estimated to be between 1.6 and 3.8 million annually in the United States (Langlois, Rutland-Brown & Wald, 2006). It is usually defined as trauma to the head resulting in a Glasgow Coma Scale score of 13-15, less than 24 hours of post-traumatic amnesia, and no evidence of intracranial abnormality on CT scan (Tellier et al., 2009). Individuals who sustain mTBI often report a constellation of symptoms, which can include symptoms such as headache, nausea, fatigue, irritability, sleep disturbance, mood swings, and anxiety, among others (King, 1997; McCrea et al., 2003; Ryan & Warden, 2003; Wiebe, Comstock & Nance, 2011). Although not severe in nature, these symptoms can interfere with the daily lives of those who experience them. In addition, there is evidence that sustaining multiple mTBIs may predispose individuals to developing a myriad of other serious health problems, including early-onset dementia, substance-use disorders, and other mental illness, which further illustrates the importance of researching the effects of mTBI in order to prevent new incidences (Canadian Institutes of Health Research, 2012). Although the vast majority of individuals who sustain a mTBI will recover within weeks to months (Frommer et al., 2006; Guskiewicz et al., 2003; McCrea et al., 2003), there is an increased risk of prolonged symptoms and for long-term consequences on health as well as on cognitive and emotional functioning after sustaining

a mTBI (Frommer et al., 2006; Guskiewicz et al., 2003; Meehan, Mannix, Stracciolini, Elbin, & Collins, 2013). Further, the odds of suffering prolonged symptoms after a mTBI are increased in those who report more symptoms after injury compared with those who report an average number of symptoms (Meehan et al., 2013).

Sex Differences in mTBI

There have been differences observed between male and female athletes after incurring mTBIs. The rates of injury of mTBI in female athletes is higher compared to male athletes (Covassin, Swanik & Sachs, 2003). In addition, females have been shown to suffer from more adverse effects after mTBI than males, including being cognitively impaired approximately 1.7 times more frequently (Broshek, Kaushik, Freeman, Erlanger, Webbe, & Barth, 2003), as well as experiencing more severe and prolonged symptoms (King, 2014). The reason that females experience higher rates of and worse outcome after mTBI is unclear, but there are multiple potential contributors. For example, females are smaller in size and generally have weaker neck muscles then men (Covassin, Swanik & Sachs, 2003). There is also evidence that the influence of the female sex hormones, particularly estrogen and progesterone, play a role in somatic, affective, and cognitive symptoms reported (King, 2014). For example, estrogen is related to migraines and anxiety and progesterone is involved with maintaining regular sleep patterns and learning novel information (Andersen, Bittencourt, Antunes & Tufik, 2006; MacGregor, Frith, Ellis, Aspinall & Hackshaw, 2006; Seeman, 1997).

Despite noted sex differences after mTBI there have been many contradictory findings as to whether or not females and males differ at baseline in terms of symptoms and neuropsychological ability (Covassin, Schatz & Swanik, 2007; Mihalik, Ondrak,

Guskiewicz & McMurray, 2009; Valovich McLeod, Bay, Lam & Chhabra, 2012). The Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) test is a commonly used baseline symptom and cognition measure. The manual indicates that there are slight gender differences in the normative data for the various subtests, which include verbal memory, visual memory, visual motor speed and reaction time (ImPACT Application, Inc., 2011). The manual also presents means and standard deviations for the Post-Concussion Symptom Scale (described in more detail below), which show slight but statistically insignificant differences between males and females at different ages (ImPACT Application, Inc., 2011). Covassin et al. (2007) also found no significant difference between the sexes on any composite scores on the ImPACT or Total symptom score. Another study found that female athletes endorse significantly more symptoms with mild severity at baseline than males (Covassin, Swanik, Sachs, Kendrick, Schatz, Zillmer & Kaminaris, 2006). To further complicate things, Frommer et al. (2011) found that after concussion, females report more neurobehavioural and somatic symptoms (i.e., drowsiness and sensitivity to noise) and that males report more cognitive symptoms (i.e., amnesia, confusion/disorientation). Frommer et al. go on to recommend that symptoms experienced after potential head injuries reported by females, even though the presentation may be different from the presentation that has been typically seen in males, should be linked to the possibility of incurring a concussion rather than assuming some other neuropsychological cause (2011).

One potential confound in this research may be the fluctuating hormonal changes in females associated with their menstrual cycles. It is widely known that females of reproductive age experience hormonal fluctuations over the course of approximately 28

days in relation to their menstrual cycles. Menstrual cycle symptoms are experienced by 20-40% of women and many of the same symptoms that are present in post-concussive syndrome are also associated with menstrual cycle phase (Archer, 2006). Despite the high incidence of menstrual cycle symptoms experienced by women, research investigating the effect of menstrual cycle phase on baseline concussion symptom reporting is limited.

The Menstrual Cycle and Hormonal Influences

There is strong evidence to support the claim that the female sex hormones estrogen and progesterone influence mood and mental function, including many of the symptoms that are assessed during athlete baseline assessments, such as difficulty concentrating, irritability, and headache, to name a few (Farage, Osborn & MacLean, 2008). Hormonal fluctuations over the menstrual cycle are suggested to modulate emotion and cognition through dopaminergic transmission (Sacher et al., 2013). There is evidence that varying concentrations of female sex hormones, estrogen and progesterone in particular, over the course of different menstrual cycle phases influence a number of brain structures including the striatum, hippocampus, thalamus, hypothalamus, insula, amygdala, frontal cortex (specifically, the inferior and middle frontal gyri), anterior cingulate cortex, and parietal areas that may all play a role in the presence of mood and cognitive symptoms (Hines, 2010; Sacher, Okon-Singer & Villringer, 2013; Fanselow & Dong, 2010; Steiner, 2003; Toffoletto, Lanzenberger, Gingnell, Sundström-Poromaa & Comasco, 2014).

The varying concentrations of female sex hormones influence the presence of symptoms differently over the course of the month (Sacher et al., 2013). The menstrual cycle is divided into phases: the follicular phase, ovulation, and the luteal phase. The

follicular and luteal phases consist of varying concentrations of the female sex hormones, including estrogen and progesterone, which can be seen in Figure 1 (Terner & De Wit, 2006; Sacher et al., 2013). The follicular phase refers to the time between the onset of menses and ovulation and the luteal phase refers to the period between ovulation and the onset of menses (Sacher et al., 2013). The menstrual cycle typically lasts about 28 days; day 1 refers to the onset of menses, which lasts approximately until day 7, and the premenstrual period lasts between days 22 and 28 (Fraser, 1985). There is evidence that eumenorrheic females (those who are experiencing normal or regular menstrual cycles and who are not taking any hormone-influencing medications) experience different brain activation patterns between the follicular and luteal phases than those females who are not eumenhorrheic (Toffoletto et al., 2014).

Progesterone concentrations are very low during menses and the early part of the follicular phase, then rise after ovulation, peaking mid-luteal phase, and falling rapidly before menses (Terner & De Wit, 2006; Sacher et al., 2013). Estrogen concentrations are also low during menses and the early part of the follicular phase, rise in the middle and late follicular phase with a peak around ovulation, remain moderate during the luteal phase, and decrease sharply before the onset of menses (Terner & De Wit, 2006). Most studies analysing changes related to the menstrual cycle compare performance during the late follicular phase (when progesterone concentrations are low and estrogen concentrations are high) with the late luteal phase (when progesterone concentrations are high and estrogen concentrations are low; Sacher et al., 2013).

Neurocognitive tasks for which women have been shown to perform better than men, such as verbal memory, are most clearly differentiated between the sexes when

females' estrogen concentrations are higher: during the luteal phase (Warren, Gurvich, Worsley & Kulkarni, 2014). Conversely, high progesterone concentrations have been observed to have negative effects on neurocognitive performance (Warren et al., 2014).

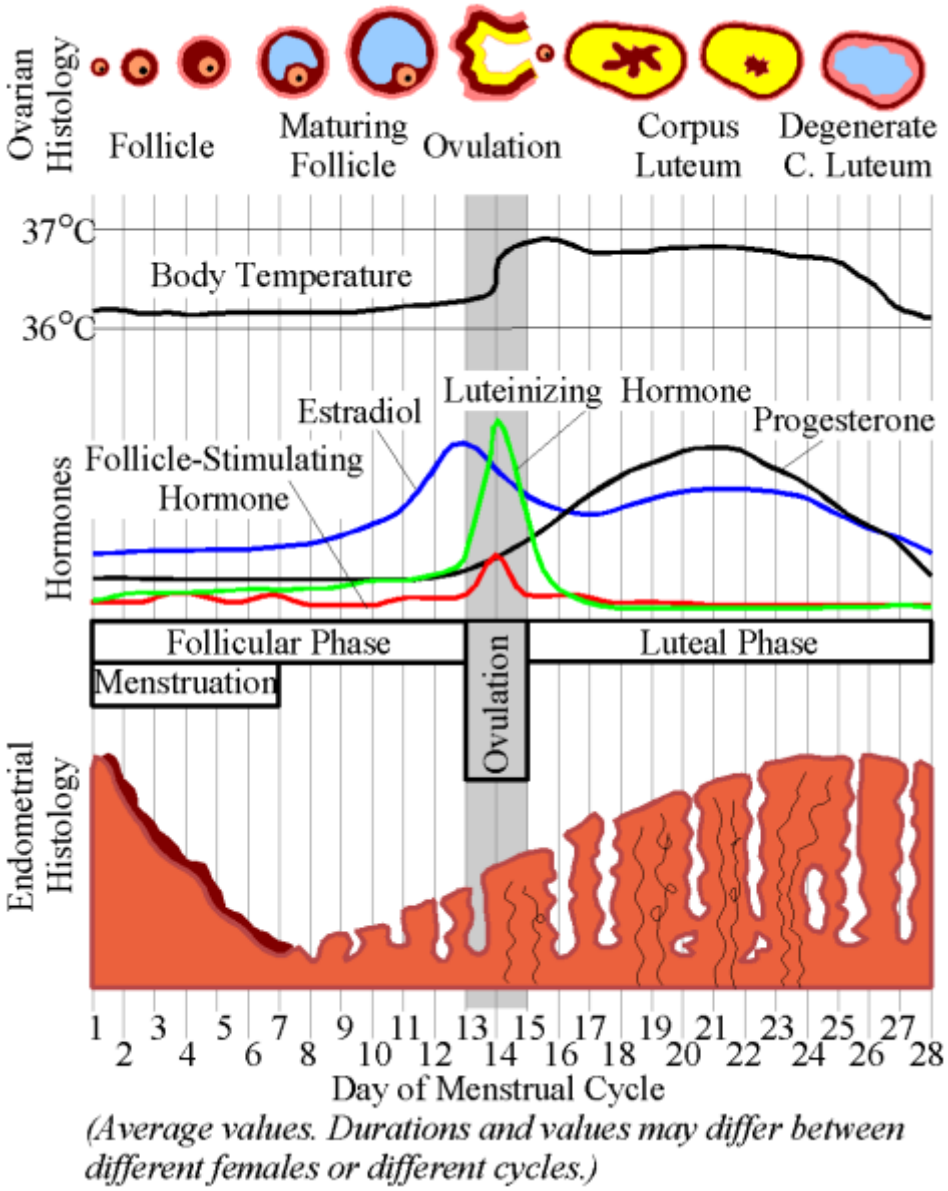

Figure 1. Hormonal fluctuations over the menstrual cycle. This Wikipedia and Wikimedia Commons image is from the user Chris 73 and is freely available at http://commons.wikimedia.org/wiki/Image:MenstrualCycle.png under the creative commons cc-by-sa 2.5 license.

Estrogen. The presence of female sex hormones, estrogen in particular, is associated with a number of somatic and affective symptoms. For example, falling concentrations of estrogen after a period of sustained estrogen presence is associated with migraines (MacGregor et al., 2006). Sixty percent of women who experience migraines link them to their menstrual cycle, but only about 8 to 14% of these are actually related to menstrual cycle phase (Case & Reid, 1998). Estrogen has also been shown to up-regulate GABA receptors, which implicates it with increasing levels of anxiety and depression (Seeman, 1997). The presence of estrogen itself has not been found to directly dampen mood, but the cyclical nature of estrogen presence in the brain and the resulting on-and-off nature of the binding of estrogen receptors has been suggested to make women more vulnerable to stress (Seeman, 1997). It is speculated that the recurrent withdrawal of estrogen may interfere with the ability to neutralize the effects of glucocorticoids released during periods of stress (Seeman, 1997).

Progesterone. The effects of progesterone have been less studied than those of estrogen. It is involved in a number of processes throughout the body, including normal sleep, mood, appetite, learning, and memory (Andersen et al, 2006).

Follicle-Stimulating Hormone and Luteinizing Hormone. These hormones are produced by the pituitary gland. Follicle-stimulating hormone causes secretions of estrogen by stimulating the growth of follicles in the ovaries, and both work to cause ovulation and the release of estrogen and progesterone (Bowen, 2004).

Overall, the influence of fluctuating sex hormones in women is known to influence many brain regions, resulting in changes to cognitive and affective processing over the course of the menstrual cycle, including levels of anxiety, depression, and

somatic complaints (Sacher et al., 2013; Seeman, 1997; Toffoletto et al., 2014). However, there are inconsistent findings about the nature and existence of specific mood changes between menstrual cycle phases in the literature (Romans, Clarkson, Einstein, Petrovic & Stewart, 2012). Some of these changes, which take place near the end of the menstrual cycle, are often referred to as premenstrual syndrome (PMS). There is no one universally agreed upon definition of PMS and it affects women differently. As such the various studies of symptoms may focus on different aspects associated the syndrome. There are over 60 instruments used to measure various symptoms related to the menstrual cycle, and many only focus on increases in the negative symptoms (e.g. irritability) rather than including information about positive symptoms (e.g. happiness) that may fluctuate over the course of the menstrual cycle (Romans et al., 2012). One study of experimentally naïve women found increases of anxiety, irritability, depression, and tension but lower reports of fatigue, confusion, sleep problems, and depression in the premenstrual phase (Parlee, 1982). Another study found that 70% of women complained of irritability, decreased morale, depression, and fatigue premenstrually (Paulson, 1961). Choi and McKeown's study of PMS symptoms revealed than many women subjectively acknowledge the experience of some symptoms, but do not believe that their symptom presentations are severe enough to be considered full-blown cases of PMS (1997).

Related to there being no one universally agreed upon definition, studies have also studied the presence of symptoms at slightly different time points within the menstrual cycle. Some research has indicated that the symptoms associated with PMS do not end as soon as menstruation occurs, but rather linger for two or three days (Romans et al., 2012).

Hormones and mTBI

The relationship between menstrual phase and outcome following mTBI is unclear. However, it has been observed that during their childbearing years females are more likely to report greater symptoms after incurring mTBI than males, suggesting the possibility that estrogen or progesterone production disruption may influence the presence of symptoms (Bazarian, Blyth, Mookerjee & McDermott, 2010). In fact, injury to the anterior pituitary gland may result in the disruption of endogenous estrogen and/or progesterone production, resulting in withdrawal of those hormones (Bazarian et al., 2010). High concentrations of progesterone have been linked with a reduction of neural impairment after mTBI whereas the findings on estrogen's influence have been mixed (Broshek et al., 2005).

Lastly, there are potentially confounding factors to consider when examining the role of menstrual cycle phase on symptom reporting in athletes, such as use of oral contraceptives and level of physical activity. These factors have been shown to influence menstrual cycle related symptomatology, as well as general symptom reporting and mood, and will be discussed next.

Oral Contraceptive Use

The use of oral contraceptives is an important consideration for research on the effects of sex hormones in women. A Canadian study found that 43% of women of reproductive age use oral contraceptives (Black, Yang, Wu Wen, Lalonde, Guilbert, & Fisher, 2009). Oral contraceptives prevent pregnancy by influencing the hypothalamic-pituitary-ovarian axis and are the most common medication prescribed to women of reproductive age (Archer, 2006). They have been found to reduce the symptoms

associated with menses, such as migraines, fatigue, and depression (Yonkers, O'Brien & Eriksson, 2008). Eumenorrheic females have been shown to endorse a higher number of symptoms and report an increased symptom severity score compared to females using oral contraceptive pills on baseline concussion testing (Mihalik, 2009). As the use of oral contraceptives reduces symptoms in women who use them, it is important to determine whether women are using them when research evaluating symptom prevalence and/or severity is being conducted.

Physical Activity

Physical activity has been shown to reduce the number and severity of general symptoms reported (Choi & Salmon, 1995) as well as PMS symptoms (Scully, Kremer, Meade, Graham & Dudgeon, 1998). Further, symptoms associated with menstruation have been shown to be reduced with the implementation of an exercise-training program (Koushkie Jahromi, Gaeini & Rahimi, 2008). Physical fitness levels have also been shown to influence the number of symptoms experienced, with higher levels of physical fitness being associated with fewer reported symptoms (Mrazik, Naidu, Lebrun, Game & Matthews-White, 2013). In particular, physical activity has been linked with a reduction in depression intensity (Nabkasorn, 2005). Therefore, it is important to consider that level of physical fitness may influence the number and severity of symptoms endorsed by an individual.

The Current Study

In sports-related concussion management programs, athletes are often assessed pre-season in order to establish a baseline level of cognitive performance as well as a baseline level of symptom reporting. It is important to consider symptoms at baseline in

order to assess whether or not the individual is ready to re-engage in physical activity, such as playing in a sporting event, after incurring a mTBI. Engaging in physical activity before the brain has had sufficient time to heal after injury can result in more severe post-concussive symptoms and a longer recovery period (Kissick & Johnston, 2005). In order to ensure that female athletes are ready to re-engage in physical activity without incurring further insult to their brains it is important to understand the relationship between the presence of symptoms at baseline and how they may vary over the course of the menstrual cycle.

The motivation for this study comes from the fact that many symptoms of PCS and PMS overlap. This study will examine how the symptoms experienced by women during different phases of the menstrual cycle overlap and relate to the symptoms typically associated with incurring a concussion by examining symptom prevalence over different stages of the menstrual cycle. It is important to understand the non-concussion related causes of these symptoms in athletes in order to help us better understand which symptoms are due to concussion versus other sources after a head injury is incurred. This study seeks to determine how appropriate it is to compare baseline symptom reports with post-concussive symptom reports of female athletes during different menstrual phases.

Hypotheses

1. It was hypothesized that the number and severity of symptoms reported on a post-concussion symptom report commonly used for baseline assessments would correlate highly with the number and severity of symptoms reported on a measure of menstrual symptoms in females in the follicular phase and again in the luteal

phase of their menstrual cycles, due to the overlapping nature of many of the symptoms experienced in both conditions.

2. It was hypothesized that women will experience fewer and less severe affective and somatic symptoms at their first testing session, which occurred during the follicular phase, and more affective and somatic symptoms during the second testing session, which occurred in the luteal phase, as concentrations of both estrogen and progesterone are increased compared with menstrual phase and symptoms typically decline at the onset of menstruation (Backstrom et al., 1983). Further, it is hypothesized that the number and severity of symptoms reported by males will remain constant at both measurement points.

CHAPTER 2

DESIGN AND METHODOLOGY

Participants

Participants for this study were recruited from the psychology participant pool at the University of Windsor. The participant pool is composed of undergraduate students who elect to take part in psychological research in exchange for extra credit in eligible courses. A total of 44 participants (31 female) were recruited. Despite the advertisement for the study saying that only women who have experienced a regular menstrual cycle (lasting approximately 28 days, for at least the past two months) may participate, four female participants reported irregular menstrual cycles and thus were eliminated from the analyses. Five women were deleted from analysis as they reported on the questionnaires being in a different place in their menstrual cycle than what they told the experimenter. Two females were fasting for Ramadan at the time of their second session (one of which was already eliminated for reporting an irregular cycle), and were eliminated from analyses due to the potential confounding effects of fasting on the symptom reports. One additional female had to be deleted due to an administration error resulting in her menstrual cycle data never being collected. Due to the fact that this was a repeated measures study, significantly more participants than were needed for analysis were sought for recruitment in an attempt to account for attrition and potential noise or invalidity in the data collected. Nonetheless, fewer than the desired number of participants signed up for the study. Three female participants and two male participants had to be eliminated from the analysis due to attrition. Thus, a total of 17 female and 11 male participants were included in analyses.

Participants received reminder emails for the study by the participant pool system the night before their appointments. Participants were incentivised with the awarding of half of a bonus point each time they spent half an hour completing the surveys, which they were able to use toward their final grade on any eligible course, as per the participant pool regulations.

The risks of participating in this study were minimal and fully explained to participants in the consent form. Questions about mood were collected as part of this study, and sometimes discussing the presence of mood symptoms can draw attention to them, resulting in psychological distress, so the questionnaires were followed with a page that included information for accessing community mental health resources for all participants.

Measures

Demographics. Participants were asked to record their age, gender, and level of education completed. This information was used for descriptive purposes and was collected using Fluid Surveys. Female participants were also asked to confirm that they have regular cycles and to record the date that their last menstrual period commenced in order to ensure that they began the study at approximately the same place in their menstrual cycle, approximately 5-7 days after the onset of their last period.

Post-Concussion Symptom Scale. The Post-Concussive Symptom Scale (PCSS; ImPACT Application Inc., 2011) questionnaire was used to evaluate the presence of some typical symptoms associated with post-concussive syndrome, such as headache, fatigue, drowsiness, and difficulty concentrating (see Appendix A for the symptom list). The PCSS is a self-report measure which uses a 7-point Likert scale ranging from "*0 - not*

experiencing" to "*6 - severe*" to rate the presence of 22 symptoms. Participants are asked to rate the severity of each symptom as they are currently experiencing it. A Total symptom score can also be calculated though combining the report of the all symptoms measured. A series of psychometric analyses demonstrated that Immediate Post-Concussion Assessment Testing (ImPACT®) Test, from which the PCSS is taken, has adequate concurrent, divergent, and convergent validity for clinical inferences of post-concussion outcome in amateur athletes (ImPACT Application Inc., 2007). Adequate internal consistency of the PCSS has been reported ($\alpha = 0.88$ to 0.94) (McLeod & Leach, 2012). The meaningful change score has been reported to be 6.8 points, indicating that a difference of approximately 7 points on the PCSS Total score at the second instance of responding to the questionnaire suggests that there is a significant difference in the number of symptoms that the person is experiencing (McLeod & Leach, 2012). Test-retest reliability has also been shown to be adequate ($r = 0.8$) (ImPACT Application Inc., 2011).

Depression Anxiety Stress Scales. The severity of depressive, anxiety, and stress symptoms was evaluated using the Depression Anxiety Stress Scales (DASS; Lovibond & Lovibond, 1995**)**. The DASS questionnaire can be found in Appendix B. The DASS is a self-report measure that consists of 42 questions answered on a Likert scale, which ranges from "*0 – did not apply to me at all*" to "*3 – applied to me very much, or most of the time*". Thus higher scores correspond with more severe symptoms. Participants are asked to rate how much the statement applied to them over the past week. After completion by the participants, the scale is divided into Depression, Anxiety, and Stress composite scores. The Depression scale evaluates the presence of symptoms typically

associated with depression, including hopelessness, anhedonia, self-depreciation, and dysphoria. Sample items from the Depression scale include statements like "*I felt that I had lost interest in just about everything*" and "*I felt I wasn't worth much as a person*". The Anxiety scale assesses situational anxiety and autonomic arousal. Sample items from the Anxiety scale include "*I was aware of the action of my heart in the absence of physical exertion (e.g., sense of heart rate increase, heart missing a beat)*" and "*I was worried about situations in which I might panic and make a fool of myself* ". The Stress scale assesses levels of chronic, non-specific levels of arousal, including becoming easily agitated, difficulty relaxing, and irritability. Sample items from the Stress scale include "*I found it hard to wind down*" and "*I tend to overreact to situations*". The DASS has a reputation for distinguishing anxiety, depression, and stress well and has adequate internal consistency and concurrent validity, with Cronbach's alphas for the Depression, Anxiety, and Stress subscales shown to be .97, .92, and .95, respectively (Antony, Bieling, Cox, Enns & Swinson, 1998). Internal consistency and temporal stability of the measure has been found to be adequate in clinically depressed samples (Page, Hooke & Morrison, 2007). The DASS has been used in clinical research of TBI and is described as a useful tool for measuring emotional status following an acquired brain injury (Dahm, Wong & Ponsford, 2013; Ownsworth, Little, Turner, Hawkes & Shum, 2008).

Physical Activity Scale. The Physical Activity Scale (PAS; Aadahl & Jørgensen, 2003**)** was used to assess participants' levels of physical activity during the previous week. The PAS was translated to English from a Danish version of the scale and has been shown to exhibit adequate face and concurrent validity (Aadahl & Jørgensen, 2003). It was selected due to its ease of administration. The scale can be found in Appendix C. To

complete the PAS, participants are asked to estimate the amount of time they spend on an average day engaging in tasks of nine different intensity levels. These nine different levels range from tasks involving very low energy expenditure, i.e. "*sleep, rest*", to high levels of energy expenditure, i.e. "*running, racing on bicycle, playing soccer, handball, or tennis*". The nine levels are associated with different levels of metabolic equivalents (MET) which estimate energy expenditure based on intensity of activity (Aadahl & Jørgensen, 2003). For each activity level measured, the MET value is multiplied by time spent on that activity, which are then added together to represent physical activity level on an average day (Aadahl & Jørgensen, 2003).

Daily Symptom Rating Scale. Female participants recorded the presence and severity of common menstrual symptoms through rating the severity of their experience of a series of symptoms at each testing session. The symptoms were measured using the Daily Symptom Rating Scale (DSRS; Taylor, 1979**)**, which can be found in Appendix D. The DSRS measures 17 symptoms typically associated with changes over the menstrual cycle and can be divided into somatic and affective indices. Symptoms were rated on a 5-point Likert scale to measure the severity of the symptoms which ranges from "*0 = not at all"* to "*5 = a very large amount"*. The DSRS was constructed from questions used on other menstrual symptom questionnaires and has been shown to exhibit adequate test-retest reliability, with all coefficients above 0.8 (Haywood, Slade & King, 2002). Criterion validity was also assessed through correlational analysis of four criteria: whether the woman had ever consulted a doctor for her symptoms, the number of tablets taken in premenstrual week, self-rating of symptom severity and estimation of severity in

relation to most women, which all significantly correlated with the DSRS Total, Affective, and Somatic scores (Haywood, Slade & King, 2002).

Menstrual Phase. Women were instructed to attend their first testing session approximately 5-7 days after the onset of their last menstrual cycle. This testing session took place during participants' follicular phase. The women then returned 14 days later for their second testing session, when they were expected to be in the midst of their luteal phase, when progesterone concentrations are high and estrogen concentrations are lower.

Procedure

Participants signed up for the study through the participant pool at the University of Windsor. Females and males signed up for separate studies on the participant pool so that the researcher had the ability to cap the number of females and/or males if the desired number of participants were reached. The research was conducted in person in Dr. Abeare's laboratory. The consent form, demographic questions, and questionnaires were presented online using Fluid Surveys. Informed consent was first obtained from all participants. Following their consent, all participants entered demographic information, including age, gender, and level of education. Females were also asked to disclose the date of the onset of their last menstrual period in order to confirm that they were commencing the study at the desired time during their menstrual cycle, as well as confirm that they have experienced a regular cycle (lasting 21 to 35 days for at least the past three months, as suggested by the Mayo Foundation for Medical Education and Research, 2016). Females were also asked do disclose if they currently use any form of hormonal contraception. Participants then completed the PAS, PCSS, and DASS questionnaires, the

order of which was randomized for each participant. Females also filled out the DSRS, which was presented in a randomized order among the other questionnaires.

The sessions took approximately twenty minutes to complete. Each participant was asked to complete the battery again at the same time of day two weeks later. Participants were emailed by the participant pool to remind them of their second appointment. They were awarded half of a bonus point each time they completed the surveys that went towards their final grade in any eligible course, as per the participant pool regulations. Female participants were asked to complete the first survey approximately 5-7 days after the onset of their last menstrual cycle and male participants were allowed to begin participation on any day they chose, as they do not have the same monthly fluctuations in hormones that females do.

CHAPTER 3

DATA ANALYSES AND RESULTS

Screening and analyses of the data were conducted using IBM SPSS Statistics Version 22. Data cleaning was completed by removing participants who did not fit the inclusion criteria. Finally, assumptions of statistical tests were assessed, including Shapiro-Wilk test, and kurtosis and skewness values for normality, and Levene's test for homogeneity of variance. Correlational analyses were conducted to examine the relationship of the PCSS and DSRS over time in the female participants. A series of 2 (time) x 2 (sex) mixed factorial ANOVAs were conducted using the various measures in order to test differences in symptom reports in both sexes over time.

Power

An a priori power analysis was conducted using the program G*Power, a free program that allows a priori power estimates to be conducted, to determine the required sample size for analysis. A power of .80, alpha value of .05, and effect size of 0.3859 were specified for the power analysis. The effect size of 0.3859 was estimated based on the findings of Gallant, Hamilton, Popiel, Morokoff and Chakraborty (1991) with respect to the effects of menstrual cycle phase on daily mood and symptoms. A sample size 18 participants of each gender was indicated. Unfortunately, this sample size was not attained and thus many of the analyses conducted had insufficient power.

Data Screening

Before any further analyses were conducted, data was assessed for missingness. There were no instances of missing data on the DSRS or DASS questionnaires. One female participant was given the wrong Fluid Surveys link, and thus demographic

information related to her menstrual phase was never collected. This participant was deleted from analyses as her menstrual phase and regularity could not be verified. One male participant did not complete the PCSS correctly at time 1 and thus his scores were not included in analyses that involved the PCSS.

The PAS data was examined, and it was found that most of the participants did not accurately rate the number of hours they spent doing the different levels of activity, as many of their responses did not add up to 24 hours. As such, the amount of time spent doing various activity levels and their MET equivalents were calculated, and then that score was prorated to account for 24 hours to yield the PAS Total score.

Visual inspection of box plots indicated that there were potential outliers on some of the questionnaires. Z scores were calculated for each questionnaire at each time point. There was one participant with a Z score of 3.10 on PCSS Total score at time 1, another participant with a DASS Anxiety Z score of 2.98 at time 2 and one other participant with a DASS Stress Z score of 2.73 at time 2. All other Z scores on all questionnaires or subscales were within 2.5 standard deviations of the means. It was decided to not remove these potential outliers as the sample size was already small, and also because these participants may represent variability in the population that is meaningful.

Two of the items on the PCSS and the DSRS are the exact same symptom. Correlational analyses of these items were evaluated between the two time points as a measure of validity. The item "headache" was positively correlated at the $p < 0.01$ level on both measures, at both time points ($r = 0.876$ and $r = 0.845$ at time 1 and 2, respectively). The item "irritability" was positively correlated at the $p < 0.01$ level on both measures at time 2 ($r = 0.845$), but it was not significantly correlated between the

measures at time 1 ($r = 0.188$). This suggests that there may be some inconsistencies in the data at time 1 threatening the validity, so findings should be interpreted with caution.

Assumptions

Originally, the use of a repeated measures multivariate analysis of covariance (MANCOVA) was planned. However, due to the small sample size and resulting lack of power, the covariance pieces of the analyses were not conducted. Thus, the assumptions of a mixed factorial analysis of variance (ANOVA) were tested, which include normality, independence of observations, and homogeneity of variance.

To investigate normality of the data, Shapiro-Wilk tests, visual inspection of scatterplots, and through examination of skewness and kurtosis cut-offs (absolute values of 2 and 3, respectively) were conducted. In the overall sample, the DASS depression subscale at time 2 was kurtotic (value = 2.47). In analysis of the females only, DASS Anxiety at time 2 was kurtotic (value = 2.36). Analysis of the male participants revealed kurtotic data on the PCSS at both time 1 and 2 (values of 4.84 and 3.42, respectively). Shapiro-Wilks analyses also revealed significant values in the overall sample for the DASS depression subscale at time 1, DASS Anxiety subscale at times 1 and 2, and DASS Stress subscale and time 2 (p's < 0.05). Analysis of the females only revealed significant values for the same variables as the overall sample, as well as DSRS Total at time 2 and Somatic subscale at time 2 (p's < 0.05). In the males only PCSS Total at time 1 and 2, and DASS depression subscale were also significant (p's < 0.05). These results suggest that the assumption of normality was violated.

Homogeneity of variance was confirmed through values on Levene's test being insignificant. It is also suggested that the highest variance value not be more than four

times the lowest variance. For the males, the highest variance value was 569.9 on the PCSS Total at time 1 and the lowest was only 8.2 on the DASS Anxiety subscale. In females, the highest variance was 294.1on the PCSS at time 2 and the lowest was 14.4 on the DASS Depression subscale at time 2. Thus, there was more variance than ideal in the data.

Independence of observations was assumed for the sex variable, as individuals in the male and female groups were all collected from different participants. No one person participated more than once. As this was a repeated measures design, the second independent variable represented time, and the same participants did participate in both instances. Repeated measures designs have the assumption of homogeneity of covariance, but seeing as this study only analyzed two different points in time this assumption is not relevant, as there are not multiple variances between more than three time points.

ANOVA is known to be robust to violations if only one of the assumptions of normality or homogeneity of variance, but in this instance both assumptions may be violated. Ideally a non-parametric test would be used instead of ANOVA, however, non-parametric tests require larger power to show significant results. As the small sample size in the current study limits the power of any analyses, it was decided to use ANOVA rather than non-parametric tests.

Demographic and Descriptive Data

Descriptive statistics for demographic variables of the sample are summarized in Table 1 below. Age and education were not found to be significantly different between the male and female groups. Correlational analysis was used to determine whether a relationship existed for age or education with PCSS or DASS scores. Age positively

correlated with PCSS at time 2 ($r = 0.42$, $p < 0.05$) and level of education was negatively correlated with the DASS Depression subscale at time 1 ($r = -0.55$, $p > 0.01$). Due to the fact that only one dependent variable was correlated with age and one with education it was deemed unnecessary to use age and education as covariates. Further, the small sample size would not have allowed for analysis of covariates. Due to the restricted ranges of age, education, and scores on the measures administered, these correlations are likely not meaningful.

Table 1

Demographic Data Means and Standard Deviations

	Age	Years of Post-Secondary School Completed
Whole Sample (N=28)	22.50 (4.08)	2.43 (1.43)
Males (N=11; 39.29%)	23.00 (4.67)	2.18 (1.47)
Females (N=17; 60.71%)	22.18 (3.76)	2.59 (1.42)

Birth Control Usage. A series of mixed factorial analyses of variance (ANOVAs) were also run using oral contraceptive use as a between subjects variable and time as a within subjects variable to determine if there was a significant difference in the between the women who use oral contraceptives, those who do not, and males on symptom reports. The dependent variables examined included the PCSS, DASS Depression subscale, DASS Anxiety subscale, and DASS Stress subscale. The analysis of the PCSS resulted in no main effect of time [$F(1, 24) = 3.45$, $p = 0.08$], oral contraceptive use [$F(2, 24) = 0.52$, $p = 0.60$], or their interaction [$F(2, 24) = 0.14$, $p = 0.87$]. Similarly, there were no significant effects on the DASS Depression subscale for time [$F(1, 25) =$

3.45, $p = 0.08$], oral contraceptive use [$F(2, 25) = 0.52$, $p = 0.60$], or their interaction [$F(2, 25) = 0.14$, $p = 0.87$]. The DASS Anxiety subscale showed significant effects for time [$F(1, 25) = 5.63$, $p = 0.03$], but not for oral contraceptive use [$F(2, 25) = 0.17$, $p = 0.85$] or the interaction [$F(2, 25) = 0.77$, $p = 0.48$]. The DASS Stress subscale also indicated significant differences on time [$F(1, 25) = 5.20$, $p = 0.03$], but not contraceptive use [$F(2, 25) = 0.34$, $p = 0.71$] or the interaction [$F(2, 25) = 0.63$, $p = 0.54$].

Mixed factorial ANOVAs were also conducted on the female participants using oral contraceptive use as an independent variable, along with time, and using menstrual symptoms as the dependent variable. Firstly, the DSRS Total was used, revealing no significant effects of time [$F(1, 15) = 3.62$, $p = 0.08$], oral contraceptive use [$F(1, 15) = 0.27$, $p = 0.61$] or the interaction [$F(2, 15) = 0.98$, $p = 0.34$]. The DSRS Affective subscale was also examined, again revealing no significant effects of time [$F(1, 15) = 1.17$, $p = 0.30$], oral contraceptive use [$F(1, 15) = 0.15$, $p = 0.70$] or the interaction [$F(2, 15) = 0.04$, $p = 0.84$]. Lastly, the DSRS Somatic subscale revealed no significant effects of time [$F(1, 15) = 3.92$, $p = 0.07$], oral contraceptive use [$F(1, 15) = 0.30$, $p = 0.60$] or the interaction [$F(2, 15) = 1.57$, $p = 0.23$]. Thus, oral contraceptive use did not significantly differentiate women on the PCSS or DSRS, or on the DASS Anxiety, DASS Depression, or DASS Stress subscales.

Physical Activity. The PAS was included with the intent to use its total score as a measure of physical activity. It was planned to be used as a covariate in the main analysis surrounding the second hypothesis, which stated that women would experience more and more severe PCS symptoms during their luteal phase compared with their follicular phase and compared with men. This was believed to be due to the fact that exercise is known to

decrease the presence of mood and other PCS symptoms (Byrne & Byrne, 1993; Leddy et al., 2010). Due to the small sample size in the study, which limits statistical power, and also due to the inconsistently correct responses on the PAS, the physical activity scale was not used as a covariate.

The PAS scores were examined to see whether they correlated with DASS subscales, PCSS Total, or DSRS Total or subscales at the same point in time. The PAS did not significantly correlate with any of the other measures at the same time point. However, PAS scores at time 1 did correlate significantly with PAS scores at time 2 (r = 0.78, $p < 0.01$), demonstrating adequate test-retest reliability.

Menstrual and Post-Concussive Symptom Correlations

Correlational analyses were also conducted between the PCSS and DSRS at each time point for female participants in order to examine the influence that menstrual related symptoms have on PCSS symptom reporting. At time 1 the DSRS Total and both subscales were all positively correlated with PCSS Total score (DSRS Total score r = 0.58, DSRS Somatic subscale r = 0.51, and DSRS Affective subscale r = 0.49, p's < 0.05). At time 2 the DSRS Total and both subscales were also all positively correlated with PCSS Total score (DSRS Total score r = 0.88, DSRS Somatic subscale r = 0.94, and DSRS Affective subscale r = 0.61, p's < 0.01). Thus the hypothesis that these two measures would be correlated was supported. PCSS and DSRS scores were also more highly correlated at time 2, when it was predicted that symptom reports on these questionnaires would be higher.

Follow-up analyses revealed that the correlation between the PCSS at time 1 and time 2 in the female participants was only 0.26, which was not significant at the $p < 0.05$

level. The DSRS Total was significantly correlated between times 1 and 2 ($r = 0.57$, $p < 0.05$). The Affective subscale was significantly correlated between the two times ($r = 0.70$, $p < 0.01$) but the Somatic subscale was not ($r = 0.43$, $p = 0.09$).

Effects of Time/Menstrual Phase and Sex on Symptom Reports

The second hypothesis was tested, which predicted that women would experience more symptoms with greater severity during the luteal phase of their menstrual cycle compared with during their follicular phase, and compared with what men experienced over two different time points. Table 2 shows the means and standard deviations of scores on the measures administered.

Table 2

Means and Standard Deviations of Measures Administered

	Females	Males
PAS 1	43.27	47.00
	(7.27)	(7.55)
PAS 2	42.73	50.74
	(10.36)	(10.32)
DASS Depression 1	5.18	6.73
	(5.25)	(6.29)
DASS Depression 2	4.35	3.55
	(3.79)	(4.37)
DASS Anxiety 1	6.00	7.09
	(5.90)	(5.65)
DASS Anxiety 2	3.71	4.18
	(4.27)	(2.86)
DASS Stress 1	13.76	11.82
	(11.35)	(8.22)
DASS Stress 2	9.88	7.18
	(8.65)	(6.18)
PCSS 1	28.00	23.80
	(15.20)	(23.87)
PCSS 2	22.82	16.45
	(17.15)	(17.03)

A series of mixed factorial ANOVAs were conducted in order to examine the effects of sex over time on symptom reporting, thus the independent variables were sex and time. The dependent variables included anxiety, depression, and stress from the DASS and the PCSS Total symptom score, which were all analyzed in separate tests. A series of univariate ANOVAs were conducted rather than a multivariate analysis of variance due to the small sample size and resulting lack of power for the analysis. Although the implementation of non-parametric statistics may have been better suited to this data, there was simply not enough power for any significant results to appear. Due to the small sample size and resulting power, as well as the unequal groups, the results of the following analyses should be considered exploratory and be interpreted with caution.

PCSS. The first mixed factorial ANOVA was conducted on PCSS scores. Neither the main effect of time nor of sex was significant [$F(1, 25) = 4.00$, $p = 0.06$ and $F(1, 25) = 0.90$, $p = 0.35$, respectively]. Nor was there a significant interaction of sex by time [$F(1, 25) = 0.26$, $p = 0.62$]. The observed power was 0.49 for time, 0.15 for sex, and 0.08 for the interaction effect. Box's M test, which is used to analyze homogeneity of variance-covariance matrices, was not significant (7.79, $p = 0.71$). This suggests that, despite the hypothesis that females would have higher reports of symptoms on the PCSS, both sexes typically report stable numbers of symptoms over time when no injury is incurred.

It was also observed that the PCSS scores in females at time 1 did not significantly correlate with PCSS scores at time 2 ($r = 0.26$). Conversely, PCSS scores of male participants were significantly correlated at time 1 and time 2 ($r = 0.87$). Given that the

test has been shown to have adequate test-retest reliability ($r = 0.8$) it is of note that the females' scores were not significantly correlated (ImPACT Application Inc., 2011).

DASS Depression. A 2 (time) x 2 (sex) mixed factorial ANOVA was conducted on DASS Depression scores. There was a main effect of time [$F(1, 26) = 4.46$, $p = 0.04$], but there was no main effect of sex [$F(1, 26) = 0.05$, $p = 0.82$]. The interaction of sex and time was also not significant [$F(1, 26) = 1.55$, $p = 0.23$]. A visual representation of the results can be seen in Figure 2 below. The observed power was 0.53 for time, 0.06 for sex, and 0.22 for the interaction effect. Box's M test was not significant (2.15, $p = 0.58$). This suggests that contrary to the hypothesis, females did not report more symptoms of depression at time 2 than males did. Rather, both sexes reported a decline in symptoms of depression over time.

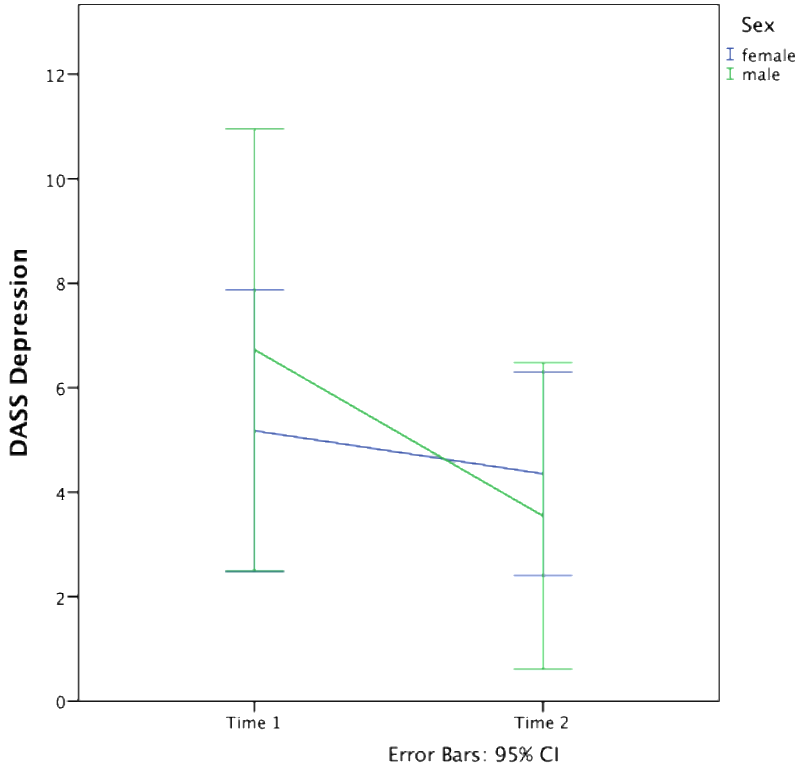

Figure 2. DASS Depression by sex and time

DASS Anxiety. A 2 (time) x 2 (sex) mixed factorial ANOVA was conducted on the DASS Anxiety subscale. There was a main effect of time [$F(1, 26) = 6.12$, $p = 0.02$], but there was no main effect of sex [$F(1, 26) = 0.25$, $p = 0.62$]. The interaction of sex and time was also not significant [$F(1, 26) = 0.09$, $p = 0.77$]. A visual representation of the results can be seen in Figure 3 below. The observed power was 0.66 for time, 0.08 for sex, and 0.06 for the interaction effect. Box's M test was not significant (2.17, $p = 0.58$). This suggests that, again, contrary to the hypothesis, females did not report more symptoms of anxiety at time 2 than males did. Rather, both sexes reported a decline in symptoms of depression over time.

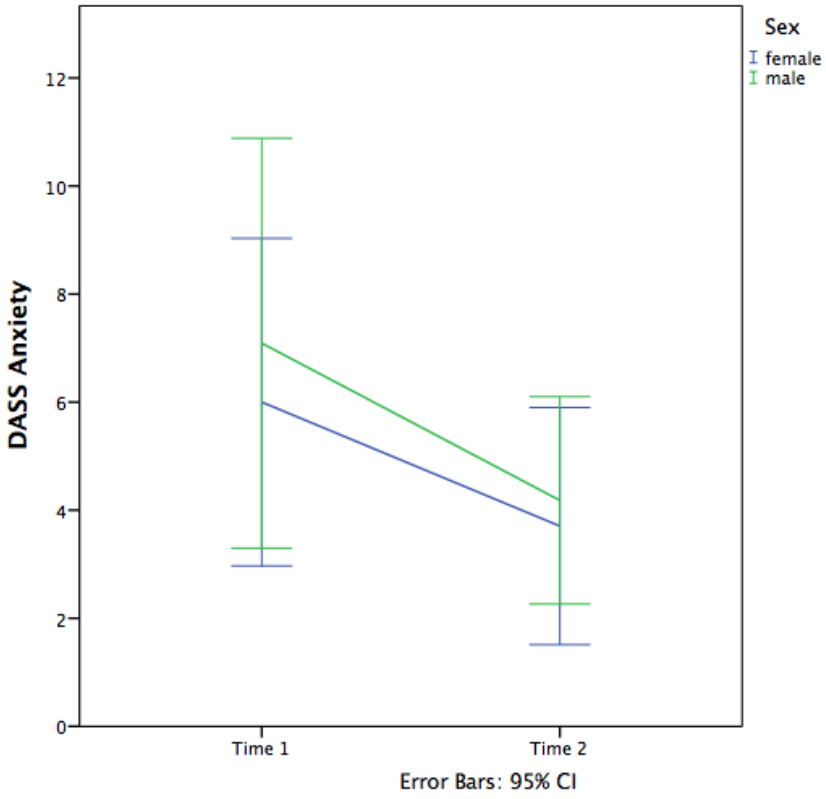

Figure 3. DASS Anxiety by sex and time

DASS Stress. A 2 (time) x 2 (sex) mixed factorial ANOVA was conducted on the DASS Stress subscale. There was a main effect of time [$F(1, 26) = 5.58$, $p = 0.03$], but no

main effect of sex [$F(1, 26) = 0.59$, $p = 0.45$]. The interaction of sex and time was also not significant [$F(1, 26) = 0.04$, $p = 0.84$]. A visual representation of the results can be seen in Figure 4 below. The observed power was 0.62 for time, 0.12 for sex, and 0.06 for the interaction effect. Box's M test was not significant (2.70, $p = 0.48$). Once again, the finding that females did not report more symptoms of stress at time 2 than males did was contrary to the hypothesis. Both sexes reported a decline in symptoms of stress over time.

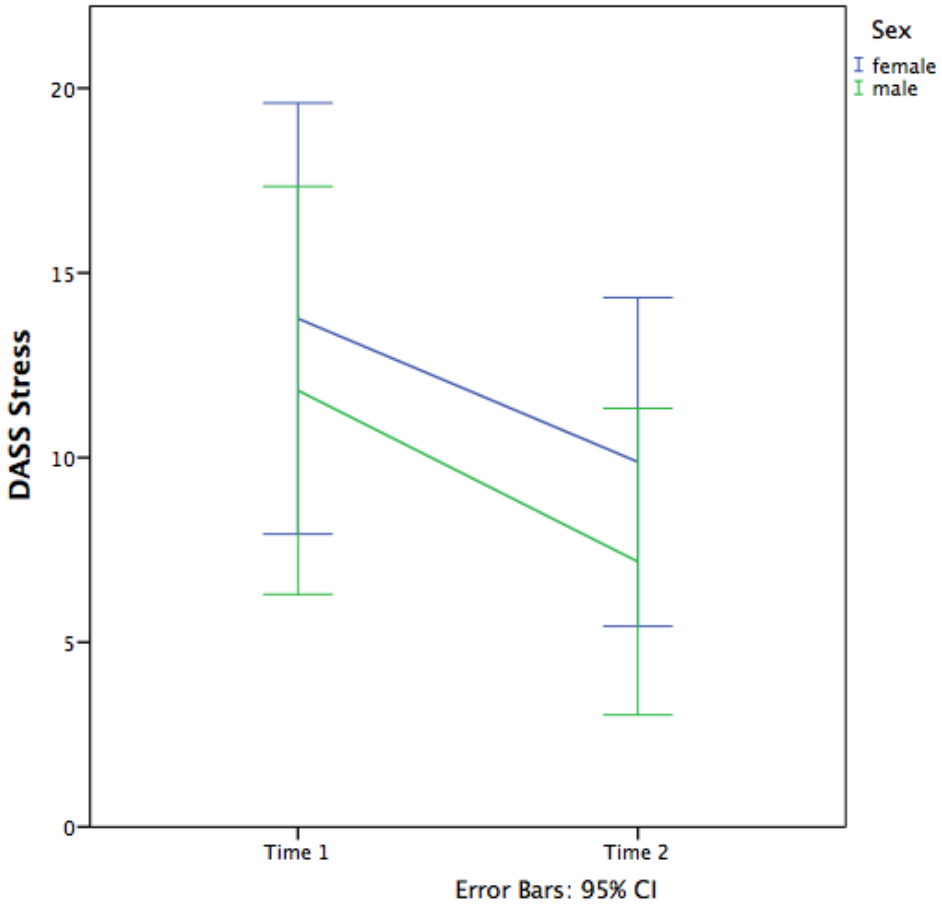

Figure 4. DASS Stress by sex and time

DSRS. A series of paired t-tests were also conducted in the female participants to determine if there was a significant effect of time on the DSRS Total score and subscales.

None of the t-tests yielded significant differences between times 1 and 2 (Total: $t = 1.97$, $p = 0.07$; Affective: $t = 1.13$, $p = 0.28$; Somatic: $t = 2.02$, $p = 0.06$). The DSRS Total was significantly correlated with itself between times 1 and 2 ($r = 0.57$, $p = 0.02$). The Affective subscale was also significantly correlated with itself between times 1 and 2 ($r = 0.70$, $p < 0.01$). The Somatic subscale was not significantly correlated between times 1 and 2 ($r = 0.43$, $p = 0.09$). DSRS Total, Affective, and Somatic subscale means and standard deviations can be seen in Table 3.

Table 3

DSRS Means and Standard Deviations Over Time

	Time 1	Time 2
Total	26.82	21.18
	(13.29)	(12.30)
Affective subscale	15.24	13.82
	(7.18)	(5.29)
Somatic Subscale	11.59	7.35
	(8.09)	(8.06)

Differences in Female PCSS Scores

Difference scores between times 1 and 2 on each item of the PCSS were calculated for the women in order to examine which symptoms in particular were decreasing over time. The top five symptoms that decreased at time 2 from reports at time 1, which all decreased 10 or more points overall, in descending order were "irritability", "feeling more emotional", "sadness", "drowsiness", and "sleeping more than usual". However, only "irritability" was significantly different at time 2 ($t = 2.67$, $p = 0.02$) and the rest of the symptoms had p values above the 95th percent confidence interval (remaining p's = 0.23, 0.10, 0.19, 0.28, respectively). The only symptoms that actually increased at time 2 were, in order of largest increase to smallest, "numbness or tingling",

"difficulty remembering", and then "feeling like 'in a fog' " and "nervous/anxious". None of these increases were significant (p's = 0.56, 0.67, 0.89, 0.86, respectively). No other PCSS symptoms were statistically significantly different between the time points.

CHAPTER 4

DISCUSSION

This study examined the relationships between reports of symptoms commonly associated with the menstrual cycle, and also those associated with incurring a concussion, over time. There were three main hypotheses that were explored and each will be discussed below.

PCS and Menstrual Symptom Correlations

The first hypothesis was that the number and severity of PCS symptoms reported would correlate at each point in time with the number and severity of menstrual symptoms reported in women. This hypothesis was investigated by examining the correlations between the PCSS Total score, DSRS Total score, DSRS Somatic subscale, and DSRS Affective subscale scores. At time 1 the PCSS Total correlated significantly with all three DSRS scores, therefore the hypothesis was supported at time 1. At time 2, the PCSS Total significantly correlated with all three DSRS scores. Thus, the hypothesis was also supported at time 2. It is interesting to note that PCSS and DSRS scores were more significantly correlated at time 2 (r = .58 at time 1 vs. r = .88 at time 2), when it was predicted that symptom reports on these questionnaires would be higher due to the increasing concentrations of female sex hormones. Fisher's Z-transformation was calculated, revealing a z score of 1.89, p = 0.03 for a one-tailed test. A one-tailed test was used due to the prediction that symptom reports on these questionnaires would be higher due to the increasing concentrations of female sex hormones. Perhaps there is some effect of menstrual phase, or the underlying sex hormones, that resulted in stronger correlations.

Effect of Menstrual Phase

It was hypothesized that women would experience fewer and less severe affective and somatic symptoms during their first testing session, occurring during the follicular phase, and more affective and somatic symptoms during the second testing session, which occurred in the luteal phase, as concentrations of both estrogen and progesterone are increased compared with during the follicular phase, and symptoms typically decline at the onset of menstruation (Backstrom et al., 1983). It was also hypothesized that male symptom reports would remain constant over time, thus resulting in an interaction effect. This hypothesis was not supported given that all of the symptom reports decreased at the second testing session, although not all of the decreases were statistically significant. Further, the interactions between the time points and genders on the participants' scores on the PCSS, the DASS Depression, the DASS Anxiety, and the DASS Stress subscales were not significant. This finding was not expected, but has the positive implication that use and comparison of these measures in females at various points in the menstrual cycle may be appropriate should these results be replicated with a larger and more representative sample. However, the observed power for these analyses related to sex were low, 0.15, 0.06, 0.08, and 0.12 for the PCSS, DASS Depression, DASS Anxiety, and DASS Stress subscales, respectively. With stronger power a potential main effect of sex may emerge. Relatedly, the observed power for the analyses related to the interaction of sex and time point were also quite low. On the PCSS power was 0.08, on the DASS Depression subscale it was 0.22, on the DASS Anxiety subscale it was 0.06, and on the DASS Stress subscale it was 0.06. Again, with stronger power there may emerge an interaction effect.

Reasons for these unexpected results may be partially explained by a number of factors. Having the male sample included in the study was helpful for interpreting these results because males do not experience a similar monthly cycle to females. As the males also showed a similar decrease in the number and severity of symptoms they reported, it suggests that the decreases in symptoms over time were not due to changes in sex hormones, but rather some other factor. Further, participants were tested at the same time of day, so daily hormonal fluctuations can be ruled out as culprits for changing levels of symptoms. In addition, participant data was collected over three semesters (winter, interim, and summer), thus time of academic year, and corresponding life stressors, should not have been a confounding factor in this study. Although, perhaps simply being further along in a semester influences students' affect and symptom presentation, as the second part of the assessment always occurred two weeks after the first.

Despite the fact that many of the symptoms measured are associated with hormonal changes over the course of the menstrual cycle, it is also possible that this study did not measure symptoms at the most opportune times to pick up differences. Female participants completed part one of the study about five to seven days after the onset of their last menstrual period, and the second part of the study was thus completed about day 19 to 21 of their cycles. Many of the symptoms measured may be more likely to increase in severity later in the luteal phase (i.e. when "premenstrual syndrome" occurs) then when measurement took place. Most symptoms thought to occur as part of the "premenstrual syndrome" only occur in the days leading up to the onset of menstruation, and potentially in the first 2-3 days of menstruation (Romans et al., 2012). It may have been better to have participants come back a few days later for their second assessment,

but due to differing schedules on different days of the week, it was thought that it would facilitate participation in the study better if appointments took place of the same day of the week, as it was desired to have participants return at the same time of day, due to daily fluctuations in hormones. It was further desired to keep the day of the week constant in case of any effects of the day of week on symptoms, in case, for example, participants were more fatigued later in the week due to attending early classes or work schedules.

Despite the lack of significant interaction between time and gender on PCSS symptoms, there are potential clinical implications. If this finding is replicable with a larger sample size, it suggests that it is appropriate to compare baseline symptom reports of females obtained in one menstrual phase with post-concussive symptom reports from a different menstrual phase without concern for elevations in number and severity of symptoms due to the menstrual cycle. That said, the different symptoms were only examined at the item level in a cursory way in this study. It is possible that the particular symptoms or types of symptoms reported may differ over time, which may be related to menstrual phase.

Relatedly, it was observed that scores on the PCSS in males were significantly correlated between time 1 and time 2 ($r = 0.87$) but we not significantly correlated for females ($r = 0.26$). While the number and severity of symptoms in the overall female sample was found not to significantly differ between time points, their scores at time 2 were not related to their scores at time 1, whereas male scores were similar to each other. This suggests that perhaps there is some effect of female sex hormones on the presence of

different symptoms at different points in the menstrual cycle rather than simply influencing the overall number and severity of symptoms.

Oral Contraceptive Use

Given the statistical limitations due to the small sample size, it is not surprising that no group differences were observed between women who do and no not use oral contraceptives (eumenorrheic women = 9 and oral contraceptive users = 8). As oral contraceptive pills are commonly prescribed to help decrease the symptoms of menstruation, the use of these pills may mask the individuals who would otherwise experience more different and more severe menstrual symptoms. However, we were unable to observe any possible effects due to limitations on statistical power related to the small sample sizes.

Limitations and Future Direction of Research

There are a number of limitations to the current study, the first and most evident being the small sample size included in the analyses. As a result of this small sample size, many of the analyses were under-powered. Conducting a similar study with an adequate number of participants may yield different results. In addition, the sample's demographics were determined through the participant pool sign up process. The results of this study may not be generalizable to non-university students, or people who did not fall into the age range of those who participated.

This study also sought to use physical activity as a covariate in analyses. Physical activity has been shown to affect the presence of the symptoms measured on the PCSS (Malleck, Richardson, Considine & Abeare, Manuscript in preparation). Due to the inconsistent reporting on the PAS, the integrity of this variable was not ideal. Participants

were likely more accurate at rating certain levels of activity rather than others. For example, the estimate for the number of hours they slept will likely be more accurate than the number of hours spent "standing, washing dishes or cooking, driving a car or truck" because the latter activities are often completed for shorter amounts of time and more often, making them more difficult to estimate than activities completes during one longer period of time, such as sleeping. PAS scores were calculated based on the percent of hours reported on the questionnaire, so the scores may have underestimated the total level of activity by participants due to underreporting of various activities while awake. Future research should further investigate the use of physical activity as a covariate with a larger sample size and more accurately measured.

When data was collected for this study the titles of the questionnaires were included due to copyright restrictions. It is unknown if participant responding was influenced by these titles. For example, it is possible that participants may have underrated symptoms on the PCSS due to the fact that they saw the word "concussion" and had not recently incurred a concussion and thus did report the presence of symptoms on this questionnaire. In future research it is advisable to remove any such titles so as to remove the possibility of biasing participant responding.

Another limitation of this study was that hormone concentrations were estimated, not directly measured. Future research could use salivary or core temperature measurements to get more accurate appraisals of menstrual phase.

Further, this study measured just two time points during the menstrual cycle. These time points were chosen as estrogen and progesterone were at different concentrations, but hormones vary continuously over the cycle, which may indicate

different concentrations of symptomatology that were not picked up on in this study. One particular time point of interest may be ovulation, after which estrogen concentrations rapidly fall. This study was not able to precisely isolate the time of ovulation due to lack of availability of direct measures of hormone concentrations. It would also be interesting to measure symptomatology later in the luteal phase, when "premenstrual syndrome" is thought to occur.

Relatedly, the same menstrual phase (follicular) was consistently measured first, as it was believed it would be easier to facilitate participant sign-up requesting first sessions take place 5-7 days after the onset of participants' last menstrual period rather than some longer period, or asking them to come in a certain number of days before their next menstrual period as they may not have known exactly when it would occur. It was feared that longer time intervals between a noticeable event (i.e. onset of menses) would introduce more variability regarding when during their menstrual cycles the females participated. Ideally, phase during the menstrual cycle when measurements took place would have also been counterbalanced to reduce any bias related to test-retest effects.

Finally, as mentioned above, this study looked simply at the number of symptoms endorsed at two different time points in the menstrual cycle rather than examining in detail which symptoms in particular, or types of symptoms (e.g. somatic, cognitive), that were endorsed at each time point. This would be of particular interest given the finding that female scores on the PCSS were not statistically significantly correlated between the time points, but the male scores were. Future research could examine the specific symptoms individually to determine if there is a difference in the particular types symptoms that are reported at different times over the menstrual cycle.

CHAPTER 5

CONCLUSIONS

This study represents an effort toward elucidating the contributing factors of menstrual phase and female sex hormones toward baseline and post-concussive neuropsychological symptoms. The results of this study indicated that female and male symptom reports were similar at different time points in the females' menstrual cycles in terms of number and severity of symptoms. The implication of these findings is that it does appear to be appropriate to compare female baseline symptom reports obtained in one menstrual phase to post-concussive symptom reports obtained from a different menstrual phase without concern that the number and severity of symptoms are due to variance in female sex hormones rather than due to the effects of the incurred mTBI. With that said, many analyses lacked power and there were also some preliminary indications that the type of symptoms experienced by women may vary over the course of the menstrual cycle. More detailed examination of types of symptoms experienced over the menstrual cycle is warranted.

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APPENDIX A

The Post-Concussion Symptom Scale (PCSS)

ImPACT™

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PATIENT'S NAME:_____

POST-CONCUSSION SYMPTOM SCALE

SEVERITY RATING
Please use this scale to rate each symptom.
None 0 | Mild 1 2 | Moderate 3 4 | Severe 5 6

Symptoms	Date:	Date:	Date:	Date:	Date:	Date:	Date:
Headache							
Nausea							
Vomiting							
Balance Problems							
Dizziness (spinning or movement sensation)							
Lightheadedness							
Fatigue							
Trouble falling asleep							
Sleeping more than usual							
Sleeping less than usual							
Drowsiness							
Sensitivity to light							
Sensitivity to noise							
Irritability							
Sadness							
Nervous/Anxious							
Feeling more emotional							
Numbness or tingling							
Feeling slowed down							
Feeling like "in a fog"							
Difficulty concentrating							
Difficulty remembering							
Visual problems							
Other							
Total							

Instructions Given for the PCSS

Please complete the paper questionnaire you were given at this time. Please indicate the level for which you are CURRENTLY experiencing the symptoms listed, as per the scale on the paper. So, you should only fill out one column with your ratings for today. Do not worry about writing the date or calculating the total. When you are finished please return to this page and click next.

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NOW THEREFORE, in consideration of the covenants, representations and warranties contained herein, and intending to be legally bound hereby, ImPACT and Customer agree as follows:

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APPENDIX B

DEPRESSION ANXIETY STRESS SCALES (DASS)

DASS

LAST NAME: FIRST NAME:

DATE:

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you over the past week [or since your recent concussion, if applicable]. There are no right or wrong answers.
Do not spend too much time on any statement.

The rating scale is as follows:
0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree, or a good part of time
3 Applied to me very much, or most of the time

Reminder of rating scale:
0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree, or a good part of time
3 Applied to me very much, or most of the time

	0	1	2	3
1. I found myself getting upset by quite trivial things	○	○	○	○
2. I was aware of dryness of my mouth	○	○	○	○
3. I couldn't seem to experience any positive feeling at all	○	○	○	○
4. I experienced breathing difficulty (eg, excessively rapid breathing, breathlessness in the absence of physical activity	○	○	○	○
5. I just couldn't seem to get going	○	○	○	○
6. I tended to over-react to situations	○	○	○	○
7. I had a feeling of shakiness (eg, legs going to give way)	○	○	○	○
8. I found it difficult to relax	○	○	○	○
9. I found myself in situations that made me so anxious I was most relieved when they ended	○	○	○	○
10. I felt that I had nothing to look forward to	○	○	○	○
11. I found myself getting upset rather easily	○	○	○	○
12. I felt that I was using a lot of nervous energy	○	○	○	○
13. I felt sad and depressed	○	○	○	○
14. I found myself getting impatient when I was delayed in any way (eg, lifts, traffic lights, being kept waiting)	○	○	○	○
15. I had a feeling of faintness	○	○	○	○
16. I felt that I had lost interest in just about everything	○	○	○	○
17. I felt I wasn't worth much as a person	○	○	○	○

Reminder of rating scale:
0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree, or a good part of time
3 Applied to me very much, or most of the time

	0	1	2	3
18. I felt that I was rather touchy	○	○	○	○
19. I perspired noticeably (eg, hands sweaty) in the absence of high temperatures or physical exertion	○	○	○	○
20. I felt scared without any good reason	○	○	○	○
21. I felt that life wasn't worthwhile	○	○	○	○
22. I found it hard to wind down	○	○	○	○
23. I had difficulty in swallowing	○	○	○	○
24. I couldn't seem to get any enjoyment out of the things I did	○	○	○	○
25. I was aware of the action of my heart in the absence of physical exertion (eg, sense of heart rate increase, heart missing a beat)	○	○	○	○
26. I felt down-hearted and blue	○	○	○	○
27. I found that I was very irritable	○	○	○	○
28. I felt I was close to panic	○	○	○	○
29. I found it hard to calm down after something upset me	○	○	○	○
30. I feared that I would be "thrown" by some trivial but unfamiliar task	○	○	○	○
31. I was unable to become enthusiastic about anything	○	○	○	○
32. I found it difficult to tolerate interruptions to what I was doing	○	○	○	○
33. I was in a state of nervous tension	○	○	○	○
34. I felt I was pretty worthless	○	○	○	○

Reminder of rating scale:
0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree, or a good part of time
3 Applied to me very much, or most of the time

	0	1	2	3
35. I was intolerant of anything that kept me from getting on with what I was doing	○	○	○	○
36. I felt terrified	○	○	○	○
37. I could see nothing in the future to be hopeful about	○	○	○	○
38. I felt that life was meaningless	○	○	○	○
39. I found myself getting agitated	○	○	○	○
40. I was worried about situations in which I might panic and make a fool of myself	○	○	○	○
41. I experienced trembling (eg, in the hands)	○	○	○	○
42. I found it difficult to work up the initiative to do things	○	○	○	○

Depression Anxiety Stress Scales

Source:
Lovibond, P. F., & Lovibond, S. H. (1995). The structure of negative emotional states: Comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. Behaviour Research and Therapy, Vol 33(3), 335-343. doi: 10.1016/0005-7967(94)00075-U, © 1995 by Elsevier. Reproduced by Permission of Elsevier.

APPENDIX C

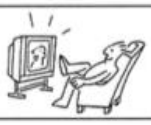
PHYSICAL ACTIVITY SCALE (PAS)

How physically active are you on an average weekday?

In the physical activity scale you see some examples of different levels of physical activity. Try to assess how much time you spend on each level on an average weekday. Start with level A and continue downward.

If you normally sleep 7 hours, you should mark the 7-h box of level A. If you watch TV for an hour and a half, you should mark the 30-min box and the 1-h box of level B. If you are not active on all activity levels, you should leave levels unmarked.

Please note that the total number of minutes and hours should amount to 24 □ an average weekday and night. You may find the column on the right helpful when adding the minutes and hours together

	Examples	Minutes	Hours	Time:
A	 Sleep, rest	□ □ □ 15 30 45	□ □ □ □ □ □ □ □ □ □ 1 2 3 4 5 6 7 8 9 10	
B	 Sitting quietly, watching television, listening to music or reading	□ □ □ 15 30 45	□ □ □ □ □ □ □ □ □ □ 1 2 3 4 5 6 7 8 9 10	
C	 Working at a computer or desk, sitting in a meeting, eating	□ □ □ 15 30 45	□ □ □ □ □ □ □ □ □ □ 1 2 3 4 5 6 7 8 9 10	
D	 Standing, washing dishes or cooking, driving a car or truck	□ □ □ 15 30 45	□ □ □ □ □ □ □ □ □ □ 1 2 3 4 5 6 7 8 9 10	
E	 Light cleaning, sweeping floors, food shopping with grocery cart, slow dancing or walking downstairs	□ □ □ 15 30 45	□ □ □ □ □ □ □ □ □ □ 1 2 3 4 5 6 7 8 9 10	
F	 Bicycling to work or for pleasure, brisk walking, painting or plastering	□ □ □ 15 30 45	□ □ □ □ □ □ □ □ □ □ 1 2 3 4 5 6 7 8 9 10	
G	 Gardening, carrying, loading or stacking wood, carrying light object upstairs	□ □ □ 15 30 45	□ □ □ □ □ □ □ □ □ □ 1 2 3 4 5 6 7 8 9 10	
H	 Aerobics, health club exercise, chopping wood or shoveling snow	□ □ □ 15 30 45	□ □ □ □ □ □ □ □ □ □ 1 2 3 4 5 6 7 8 9 10	
I	 More effort than level H: Running, racing on bicycle, playing soccer, handball or tennis	□ □ □ 15 30 45	□ □ □ □ □ □ □ □ □ □ 1 2 3 4 5 6 7 8 9 10	

Malayna Malleck Dec 1, 2015

Hello Dr. Aadahl,

My name is Malayna Malleck and I am a master's student in clinical neuropsychology at the University of Windsor in Canada. I am looking for a simple measure to add into my master's thesis study that will measure physical activity so that I can use it as a covariate. My study is going to assess how appropriate it is to compare baseline concussion symptom scores obtained by women during one menstrual cycle phase with post-concussion symptoms measures obtained during a different menstrual phase. I read your article about the physical activity scale and I think that your measure would be a good fit for my study. Would it be okay with you for me to use your measure please?

If you have any questions about the study please ask.

Best,
Malayna

Mette Aadahl to you Dec 2, 2015

Dear Malayna,
Thank you for your interest in our physical activity questionnaire. You are indeed very welcome to use it. Good luck with your study!
Best,
Mette Aadahl

APPENDIX D

DAILY SYMPTOM RATING SCALE (DSRS)

Please record your experience during this day of the feelings and sensations listed below.

Daily Questions

	0 not at all	1 very little	2 little	3 moderate amount	4 large amount	5 very large amount
1) Hopelessness						
2) Depression						
3) Lack of initiative						
4) Withdrawal						
5) Tension						
6) Irritability						
7) Argumentativeness						
8) Cheerfulness						
9) Outgoingness						
10) Energy						
11) Breast swelling or tenderness						
12) Abdominal swelling						
13) Swelling of face, hands, ankles						
14) Pelvic or abdominal pain						
15) Backache						
16) Headache						
17) Tiredness						

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