AUTONOMIC STRESS RECOVERY AND HABITUATION IN MIGRAINE

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Migraine sufferers have been characterized as particularly "stress-sensitive," and they tend to experience headaches following periods of increased psychological stress. The biological mechanisms responsible for this unusual stress response are poorly understood. In particular, it is unclear why migraineurs suffer from headaches in response to stress while others do not. Several theories have implicated autonomic dysfunction—and in particular, sympathetic hyper-reactivity to stress— as a way of explaining increased psychological stress reactivity found in migraineurs. Despite efforts to capture these patterns in laboratory stress settings, researchers have been largely unable to provide reliable evidence of autonomic hyper-reactivity to acute stress in this population.

The present study pursued the alternative hypothesis that migraineurs have prolonged autonomic recovery following stress, along with decreased habituation to repeated stressors. We compared patterns of autonomic stress recovery and habituation in a sample of young adult migraineurs and healthy controls using a repeated intermittent stressor task and separate measures of sympathetic and parasympathetic function. In contrast to our predictions, which posited sustained sympathetic engagement and a possibly blunted parasympathetic rebound upon stressor cessation, we found that individuals with episodic migraine were largely indistinguishable from controls in their sustained stress responses. Unexpectedly, migraineurs

demonstrated consistently stronger vagal withdrawal to repeated stressors than healthy controls. They also showed evidence of greater cognitive and emotional reactions than controls, primarily in the form of higher subjective stress and more negative appraisals of the stressor task itself. While this is not the first study to report altered parasympathetic function in migraineurs, it is one of only a handful to assess these patterns in the context of acute laboratory stress exposure, and the only known study to report exaggerated parasympathetic withdrawal alongside reports of increased subjective stress and negative stress appraisals.

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1.0 INTRODUCTION

Psychological stress is one of the most common triggers for migraine attacks (Sauro & Becker, 2009). Characterizing how the stress response differs in people who suffer from migraines and those who do not could be crucial to understanding some of these mechanisms and identifying appropriate targets for intervention. The present study investigated differences between migraineurs and non-migraineurs in their autonomic stress responses, as well as cognitive factors that may help explain these differences. In particular, we focused on patterns of sustained stress reactivity, including recovery and habituation to repeated stress.

Individuals who suffer from migraines are thought to be "stress-sensitive" and have been described in the clinical literature as hyper-reactive to stressful events and stimuli (Henrich & Huber, 2003). Research on the underlying physiological mechanisms of stress sensitivity in migraineurs has included several studies exploring the role of dysfunctional autonomic reactivity.

The autonomic nervous system (ANS) plays an important role in the physiological threat response, and through its interacting sympathetic and parasympathetic branches, the ANS helps generate flexible responses to environmental stressors. The ANS has also been implicated in the modulation of pain, and several theorists have identified mechanisms by which exaggerated or inflexible autonomic responses to stress could contribute to subsequent headaches in migraineurs (Pietrobon & Moskowitz, 2013; Sauro & Becker, 2009). Unfortunately, empirical studies using laboratory stressors have failed to show reliable patterns of acute autonomic hyper-reactivity to

stress in migraineurs (Cohen, Rickles, & McArthur, 1978; Leijdekkers & Passchier, 1990; Stronks et al., 1998). Rather, these studies have shown more reliable elevations in migraineurs' autonomic responses during the post-stress recovery period (e.g., Hassinger, Semenchuk, & O'Brien, 1999b), indicating that they may have an abnormally sustained response to stress. Migraineurs also show diminished habituation to repeated presentations of stressful stimuli according to electrocortical and some autonomic indices (Ambrosini & Schoenen, 2003; Huber, Henrich, & Gündel, 2005).

Together, these findings provide some evidence that autonomic stress responses among migraineurs are better characterized by their inflexibility and failure to show adaptive decreases over time rather than having greater initial magnitude. A shift from the notion of acute "stress sensitivity" to an emphasis on sustained stress reactivity could have important clinical implications for migraineurs, particularly given the ongoing, repetitive nature of psychological stress exposure in day-to-day life. Unfortunately, previous laboratory stress studies in this literature have been more focused on the role of acute stress reactivity and have used methods that are not ideally suited for the investigation of autonomic recovery and habituation. Those studies that have examined these phenomena have mostly used more generalized measures of autonomic function that do not differentiate between sympathetic and parasympathetic dysfunction, such as blood pressure (e.g., Domingues, Fonseca, Ziviane, Domingues, & Vassalo, 2010), pulse amplitude (e.g., Drummond, 1982), or heart rate (e.g., Huber et al., 2005). Such information could be useful in designing targeted interventions that could be utilized following stressor exposure but before the onset of a migraine attack.

The present study aimed to compare patterns of autonomic recovery and habituation to repeated psychological stress in migraineurs and healthy controls using a repeated laboratory

stressor paradigm and separate measures of sympathetic and parasympathetic function. Furthermore, in an effort to link autonomic mechanisms with psychological functioning in migraineurs and to help identify potential targets for intervention, we sought to examine the role of key stress-related cognitive variables (e.g., appraisal and perseverative cognition) in explaining these patterns.

1.1 AN INTRODUCTION TO MIGRAINE

A diagnosis of migraine without aura from the second edition of the International Classification of Headache Disorders (ICHD-2) requires all of the following symptoms: a) recurrent headaches (at least 5 lifetime attacks); b) untreated or unsuccessfully treated headache duration of 4 to 72 h; c) at least two of the following pain characteristics: unilateral, pulsating, moderate or severe intensity, or aggravated by routine physical activity; and d) during headache attacks, at least two of the following additional symptoms: nausea and/or vomiting, photophobia, and or phonophobia. In addition, the headaches cannot be attributable to another medical condition.

Individuals who meet diagnostic criteria are further subdivided into those with and those without aura. A diagnosis of migraine with aura includes the additional criteria that patients experience one or more aura symptoms indicative of cerebral cortical or brain stem dysfunction (i.e., visual disturbances, unusual tactile sensations) for up to 60 minutes immediately before the onset of headache symptoms.

Individuals meeting criteria for migraine diagnosis vary widely in the frequency of their migraine attacks, and researchers have found it useful to differentiate between episodic migraine

(i.e., <15 headache days/month) and chronic migraine (15 or more headache days/month). Although the use of this specific cutoff score is admittedly somewhat arbitrary (Katsarava, Buse, Manack, & Lipton, 2012), the distinction between episodic and chronic migraine appears to identify distinct groups that differ in epidemiologic and symptom profiles, rates of treatment seeking, medication usage, and comorbidity with other physical and psychological conditions (Cady, Schreiber, & Farmer, 2004; Katsarava et al., 2012). While psychological stress has also been identified as a factor in the development and maintenance of chronic migraine, other factors considered central include medication overuse, caffeine, and obesity. Given the more intermittent nature of headaches in episodic migraineurs, these individuals are more suitable participants for the present study, as they are more likely to have identifiable triggers (e.g., stress) for individual migraine attacks, and are less likely to be taking medications that would directly impact autonomic function.

1.1.1 Relevant Theory of Migraine Pathophysiology

There are numerous theories of migraine pathophysiology and a growing body of research delineating likely mechanisms underlying the pain and other symptoms that occur during a migraine attack (Burstein & Jakubowski, 2005). It is beyond the scope of the present paper to describe all historical theories of migraine development; however, the present section contains a brief overview of prominent theoretical ideas that may directly link variables explored in the current study (namely autonomic function) to subsequent migraine attacks.

1.1.1.1 Vascular theories. Up until the past two decades, the most popular theories of migraine pathophysiology tended to focus on dysfunction in the vasculature, implicated exaggerated or unstable vasomotor responses (e.g., vasoconstriction and vasodilatation) as the primary source of dysfunction in migraine (Olesen, 1987). Some very early vascular theories included hypothesized interactions with the ANS, such as the model put forth by Latham (1872), which posited that exhaustion of the SNS could lead to vasodilation that in turn produced the head pain of a migraine. Empirical studies subsequently refuted the notion of direct sympathetic involvement, and more recent accounts of vascular involvement have instead focused on the initiating role of irritated sensory neurons in the extracranial tissue (Borkum, 2012). Overstimulation of these neurons promotes the release of local inflammatory chemicals that stimulate vascular changes.

Vascular theories that exclude other prominent factors have become less popular with the arrival of evidence that many vasodilators failed to induce migraine, while others produced migraine without any cerebral vasodilation (Kruuse, Thomsen, Birk, & Olesen, 2003; Rahmann et al., 2008). Altogether, empirical research indicates that, while they are frequently present during or prior to migraine attacks, vascular changes alone are not sufficient to explain headache pain during a migraine attack.

1.1.1.2 Neural theories. More recently, neural theories have emerged that emphasize dysfunction of the central nervous system in migraine pain as well as other symptoms preceding and during a migraine attack (e.g., Welch, D'andrea, Tepley, Barkley, & Ramadan, 1990). Some neural theories have tried to account for prodromal symptoms and other symptoms present during the migraine, many of which appeared to be autonomic in origin (e.g., body temperature changes, gastrointestinal distress, fatigue, dizziness; (Kelman & Tanis, 2006). These theories

relied heavily upon experimental evidence of increased neural excitability in migraineurs to changes in the internal environment (e.g., homeostatic shifts) or external environment (e.g., sensory stimuli). The notion of migraineurs as having a "sensitive brain" is largely a product of research in this area. Neural theories have proven particularly useful in explaining some specific migraine-related phenomena—such as aura and cortical spreading depression (CSD)—that are present in only a minority of migraine sufferers, thus limiting the applicability of this information. Newer adaptations of neural theories have provided broader models in which neural excitability in the cortex produces a diverse array of migraine symptoms through activation of brainstem nuclei (Goadsby, Lipton, & Ferrari, 2002). These nuclei serve as hubs for ascending and descending pathways implicated in the transmission of head pain (e.g., the trigeminovascular system), sensory signals (e.g., the locus coeruleus), and autonomic control (e.g., the nucleus solitarius and nucleus ambiguus).

While these theories provide probable loci for the emergence of diverse migraine symptoms, debate continues about the order and necessity of various steps in the initiation of a migraine attack (Goadsby et al., 2002; Spierings, Ranke, & Honkoop, 2001). In addition, while these theories are good at explaining how certain triggers (e.g., intense stimuli) may lead to certain migraine symptoms, they do not account well for the relationship between stress and migraines.

1.1.1.3 Integrated neurovascular theories. More modern theoretical accounts of migraine pathogenesis include components of both vascular and neural theories, while integrating the potential role of inflammation, endocrine responses, and neurophysiological factors. An example of such an integrative account is that put forth by Drummond and Passchier (2006). They hypothesize that migraineurs have abnormalities in the serotonin system that make them

especially sensitive to environmental stimuli and their central nervous systems in turn highly susceptible to increased arousal. In these individuals, the resulting release of corticotrophin-releasing hormone in response to intense stimulation leads to increased inflammation, triggering vascular changes and sensitizing the body to pain.

The brainstem continues to be a central focus of evolving conceptualizations of migraine pathogenesis, and one particular brainstem structure that has received increasing attention for its involvement in the association between psychological stress and migraine is the midbrain periaqueductal grey (PAG). Historically, this area has been most closely associated with its role in anti-nociceptive processing, however it also has numerous connections with the ANS and with somatic motor systems mediating patterned behavioral responses to threat. The PAG seems to become overly-active in migraine patients, a pattern which may either reflect or result in a paradoxical reversal in its pain-reprocessing function, whereby it now amplifies pain signals, particularly those coming from the trigeminovascular system.

1.1.1.4 Missing pieces of the theoretical puzzle. An important conclusion that can be taken from this overview is that much of the theory around migraines has focused on phenomena (e.g., vasodilation or constriction in vascular theories, CSD in neural theories) that are only associated with migraine some of the time, that not all migraineurs experience, and that are not sufficient to explain the relationship between common triggers and migraine attacks. There is increasing recognition within the medical community that, to understand migraine, it is important to consider factors that influence the threshold of a person's susceptibility to a migraine attack, as well as the mechanisms that trigger the attack. One popular notion in the recent literature is the notion that migraineurs have triggers that lower their threshold for headache initiation below that of a non-migraineur (Burstein & Jakubowski, 2005). From this perspective, a so-called trigger is

not necessarily a specific event or discrete stimulus, but some internal or external factor that shifts a person's "set point" and alters the way he or she processes and adapts to subsequent stimuli. Many of the most common migraine triggers (e.g., sleep deprivation, hormonal shifts, not eating, dehydration) appear to involve shifts in homeostatic functions that leave an individual increasingly sensitive to subsequent triggers.

1.1.2 Migraines and Stress

Stress is one of the most frequently reported triggers for migraine attacks. Approximately 70-80% of migraineurs report stress as a common trigger for their attacks (Hauge, Kirchmann, & Olesen, 2010; Kelman, 2007; Spierings et al., 2001), with close to half reporting that stress is their primary trigger (Zivadinov et al., 2003). Psychological stress has also been known to exacerbate existing headache episodes (Spierings et al., 2001), and one study even found that migraine attacks preceded by stress were experienced as subjectively more painful than attacks preceded by other triggers (Chabriat, Danchot, Michel, Joire, & Henry, 1999). Prospective studies using experience sampling and daily diary methodologies further support the notion that migraine attacks are frequently precipitated by psychological stress (Hashizume et al., 2008; Holm, Lokken, & Myers, 1997; Köhler & Haimerl, 1990; Schoonman et al., 2007; Spierings, Sorbi, Maassen, & Honkoop, 1997). It is because of findings like these that behavioral interventions for migraine are aimed at managing stressors and patients' responses to them (Holroyd, 2002).

Several researchers have reported on the lagged relationship that frequently exists between stress and migraine attacks, with headaches occurring typically hours or even a day after perceived stressors (Holm, Lokken, et al., 1997; Köhler & Haimerl, 1990; Schoonman et al., 2007; Spierings et al., 1997). Migraine onset often takes place during periods of relaxation

following stress (Hashizume et al., 2008; Spierings et al., 1997). Accordingly, processes occurring after stressor offset may be particularly relevant for the subsequent onset of headaches; a more sustained physiological stress response could serve as a more proximal migraine trigger than the acute stress response (Nash & Thebarge, 2006). Additional support for the role of sustained stress response in migraine comes from research indicating that, while migraines can be triggered by a single stressful event, they more often follow an overall increase in perceived stress and/or greater frequency of daily hassles and interpersonal stressors in the day or days preceding an attack (Köhler & Haimerl, 1990; Levor, Cohen, Naliboff, & McArthur, 1986; Schoonman et al., 2007). Furthermore, individual stressors are more likely to be followed by an attack if the individual was already feeling tired, tense, and/or irritable when the stressor took place, suggesting that they may not have recovered fully from previous stressors (Spierings et al., 1997).

Migraineurs have been characterized in the clinical literature as being particularly sensitive to stress. Relative to non-headache controls, they score higher on self-report measures of stress susceptibility and reactivity (Hedborg, Anderberg, & Muhr, 2011; Rojahn & Gerhards, 1986). Some studies have shown that migraine patients are more likely to endorse personality traits characterized by increased behavioral and/or emotional reactivity to threat, such as neuroticism (Henrich & Huber, 2003) or harm avoidance (Abbate-Daga et al., 2007; Sánchez-Román et al., 2007). With regard to their responses to acute laboratory stressors, migraineurs have reported greater subjective stress, tension, and fatigue during cognitive stressors than do healthy controls (Hassinger et al., 1999b; Huber et al., 2005). However, not all studies have found greater self-reported anxiety in response to acute laboratory or real-life stress (Passchier, Goudswaard, & Orlebeke, 1993). In fact, several studies have reported no group differences

between migraineurs and healthy controls on measures of subjective stress sensitivity (Gunel & Akkaya, 2008; Kröner-Herwig, Ruhmland, Zintel, & Siniatchkin, 2005), particularly when these measures are trait rather than state-specific.

In contrast to the basic notion of greater stress sensitivity, the idea that migraineurs may have a prolonged stress reactivity has been less directly explored. There is, however, some preliminary evidence to suggest that they struggle to calm down or relax after stressor cessation. Compared to headache-free controls, migraineurs report higher levels of anxiety and subjective stress reactivity during laboratory post-stress recovery periods (Huber et al., 2005; Kröner-Herwig, Fritsche, & Brauer, 1993). The clinical literature has also tended to portray migraine-sufferers in ways that suggest difficulty psychologically disengaging from stressful stimulation. The so-called "migraine personality" is typified by terms such as "rigid", "persistent", "perfectionistic" and qualitative accounts have described sufferers as maintaining a continuous "state of readiness" (Rutberg & Öhrling, 2012). Migraineurs have also demonstrated difficulty habituating to stressful situations, such that they continue to experience higher levels of subjective distress in the presence of a repeated or continuous stressor, while non-migraineurs demonstrate habituation or adaption (Borsook, Maleki, Becerra, & McEwen, 2012).

1.1.3 The Autonomic Stress Response: Potential Dysfunction in Migraine

One biological system that is central to rapid and flexible responses to stress is the ANS. The ANS maintains homeostatic control over the body, generating adaptive physiological responses to shifts in internal bodily states and changing environmental demands. The ANS exerts control primarily through two branches: the SNS and the parasympathetic nervous system (PNS). The SNS serves as the excitatory division of the ANS, and it is largely responsible for generating arousal responses that prepare the body for immediate action. The SNS coordinates many of the

rapid physiological changes observed during responses to acute stress, including cardiac (e.g., increased heart rate), vascular (e.g., vasoconstriction), and sudomotor (e.g., sweat production) changes. In contrast, the PNS primarily initiates restorative functions and helps return the body to resting metabolic levels after the need for immediate action has passed. It promotes actions, such as decreases in heart rate and contractile force, and increases in digestion and peripheral blood flow. To this end, dysfunction in one or both branches of the ANS can bring about unusually elevated or otherwise maladaptive long-term responses to stress (Thayer, Yamamoto, & Brosschot, 2010; Vella & Friedman, 2007). Autonomic dysfunction has been linked to a number of stress-related chronic health conditions, including cardiovascular disease (Thayer et al., 2010)

1.1.3.1 General autonomic function in migraineurs. The ANS has long been postulated to be involved in migraine pathogenesis. This may be in part because of the autonomic-like symptoms that some patients experience before, during, or after headache attacks (Feuerstein, Bortolussi, Houle, & Labbé, 1983), including fatigue, gastrointestinal disturbance, sweating, and/or pupil dilation. Prophylactic medications for migraine also tend to have an effect on ANS function (Gass & Glaros, 2013). Given its role in modulating bodily states in response to environmental changes, researchers have hypothesized that the ANS may function abnormally in migraineurs, and that these abnormalities may play a role in the development of migraine attacks (Gass & Glaros, 2013).

Because it is possible that autonomic dysfunction in response to psychological stress in migraineurs could reflect more general abnormalities in the ANS, it is worthwhile to discuss findings from the broader research on ANS function in migraine. Research comparing migraineurs and non-migraineurs on tonic (e.g., “baseline”) autonomic functioning has produced

ambiguous and contradictory results. Among studies that have used more general indicators of ANS "arousal" (i.e., heart rate, blood pressure, etc.), some have reported slight hyperarousal (Stronks et al., 1998), others have found normal levels of autonomic arousal (Hassinger et al., 1999b; Holm, Lamberty, McSherry, & Davis, 1997), and still others have reported hypo-arousal in migraineurs relative to controls (Gotoh, Komatsumoto, Araki, & Gomi, 1984; Havanka-Kanniainen, Tolonen, & Myllylä, 1988). Similarly, studies that have used more specific cardiac, electrodermal, and cholinergic measures of tonic SNS function have reported sympathetic hypofunction (Gotoh et al., 1984; Peroutka, 2004), mild to moderate hyperfunction (Appel, Kuritzky, Zahavi, Zigelman, & Akselrod, 1992; Perciaccante, Fiorentini, Valente, Granata, & Tubani, 2007; Stronks et al., 1998), and normal SNS function in migraine sufferers (Passchier et al., 1993). Research on tonic PNS function have produced reports of both hypofunction (Havanka-Kanniainen et al., 1988; Perciaccante et al., 2007; Tabata et al., 2000) and normal function (Appel et al., 1992; Martín et al., 1992) in migraineurs. Thus, studies using resting measures of ANS function have failed to produce a consensus on this issue.

Because abnormalities in migraineurs' ANS function may only be evident in response to some perturbation, several researchers have probed for abnormalities in autonomic reactivity in response to traditional physiological challenges. These challenges include deep breathing, the Valsalva maneuver (i.e., forced expiration), the orthostatic tilt-test, and isometric tests, such as sustained hand-grip, and all are designed to produce reflexive adaptive responses in the SNS and/or PNS. Initial studies using these challenges reported decreased SNS reactivity (Gotoh et al., 1984; Havanka-Kanniainen, Tolonen, & Myllylä, 1986; Havanka-Kanniainen et al., 1988), particularly in migraine with aura, and in migraineurs with more chronic headaches (Havanka-Kanniainen et al., 1988), although there have been more recent reports of normal SNS reactivity

relative to healthy controls (Cortelli et al., 1991; Pogacnik, Sega, Pecnik, & Kiauta, 1993). Studies of PNS function during these same maneuvers (typically indexed by measures of cardiovascular variability) have also produced conflicting results, with some authors reporting blunted PNS responses (Gotoh et al., 1984; Havanka-Kanniainen et al., 1988; Thomsen, Iversen, Boesen, & Olesen, 1995), and others reporting normal PNS responses in migraineurs (Martín et al., 1992; Pierangeli et al., 1997).

Another class of physiological challenges in the literature are those that have exposed migraineurs to painful or uncomfortable sensory stimuli and compared their autonomic responses to those of healthy controls. Notably, migraineurs typically fail to differ from controls in autonomic reactivity to laboratory pain stimuli (Domingues et al., 2010; Drummond, 1982; Feuerstein et al., 1983; Hassinger et al., 1999b; Kröner-Herwig et al., 1993; Leistad et al., 2008). Research exposing migraineurs to noxious auditory and visual stimuli has typically found no alterations in reactivity on electrodermal and peripheral cardiac measures (Bäcker et al., 2001; Ellertsen & Hammerborg, 1982; Ellertsen, Nordby, Hammerborg, & Thorlacius, 1987; Huber et al., 2005; Kröner-Herwig, Diergarten, Diergarten, & Seeger-Siewert, 1988; Passchier & Orlebeke, 1983), although a few studies have reported slower habituation of cerebral vascular responses in migraineurs when stimuli were presented repeatedly (Bäcker et al., 2001; Nedeltchev et al., 2004; Passchier & Orlebeke, 1983). Finally, studies that have examined autonomic recovery from pain or noxious sensory stimuli have also failed to find differences between migraineurs and controls (Hassinger et al., 1999b; Huber et al., 2005).

To summarize, laboratory studies using tonic measures or traditional physiological challenges to assess ANS function in migraineurs have produced highly inconsistent results. Comparisons with healthy controls on sympathetic measures have produced findings in both

directions, as well as null findings, while comparisons of parasympathetic function have indicated no group differences or possible hypofunction in migraineurs. Some of these inconsistencies may emerge from the use of differing patient samples with varying degrees of migraine severity and chronicity. There is, for instance, some indication that certain patient subtypes (i.e., migraine with aura, chronic migraine) are more prone to sympathetic hypo-responsivity. However, efforts to form a coherent picture of general autonomic dysregulation in migraineurs as a whole have been unsuccessful. In contrast to the conflicting findings from studies of more traditional autonomic tests, migraineurs appear to have relatively normal ANS responses to pain and noxious sensory stimuli across studies. One exception appears to be their pattern of habituation to repeated presentations of sensory stimuli, a pattern that mirrors findings from studies of electrocortical potentials in migraineurs.

1.1.4 Autonomic Responses to Psychological Stress in Migraineurs.

1.1.4.1 Acute reactivity. Previous studies of acute cardiac, vascular, and/or electrodermal reactivity to laboratory stressor tasks have produced contradictory findings. Several early studies reported greater stress reactivity in migraineurs (Cohen et al., 1978; Drummond, 1982; Gannon, Haynes, Safranek, & Hamilton, 1981; Passchier et al., 1993; Rojahn & Gerhards, 1986), particularly on measures of peripheral vascular response. Because blood vessels are primarily innervated by postganglionic sympathetic neurons, vascular responses to increased metabolic demands brought on by stress were initially thought of as clear evidence of autonomic involvement in migraineurs' stress-response abnormalities.

However, among studies reporting group differences in peripheral vascular responses, some found evidence of greater vasoconstriction relative to controls (Drummond, 1982; Passchier et al., 1993; Rojahn & Gerhards, 1986), while others reported greater vasodilation

(Gannon et al., 1981). Many more researchers have found no significant group differences in the magnitude of peripheral vascular reactivity during psychological stressors (Cohen et al., 1978; Kröner-Herwig et al., 1988; Leijdekkers & Passchier, 1990; Thompson & Adams, 1984). Measures of cardiac responsivity to stressors have produced similarly ambiguous results, with a few studies reporting greater increases in heart rate, blood pressure in migraineurs, while others have failed to find group differences in reactivity (Cohen et al., 1978; Domingues et al., 2010; Kröner-Herwig et al., 1988; Leijdekkers & Passchier, 1990; Passchier et al., 1993; Stronks et al., 1998). The majority of studies that have examined electrodermal responses (i.e., skin conductance), which is thought to index SNS activity more directly, have also failed to find group differences in stressor reactivity (Cohen et al., 1978; Kröner-Herwig et al., 1988; Passchier et al., 1993).

1.1.4.2 Recovery. While most of the studies investigating physiological stress responses in migraine have focused on reactivity during an acute stressor, a smaller number have examined the post-stress recovery period. A small but growing body of research indicates that autonomic recovery from psychological stressors, such as mental arithmetic or a speech task, is impaired in migraine sufferers (Arena, Blanchard, Andrasik, Appelbaum, & Myers, 1985; Gannon et al., 1981; Hassinger et al., 1999b; Holm, Lamberty, et al., 1997; Huss, Derefinko, Milich, Farzam, & Baumann, 2009).

Many findings in this area have come from studies using non-specific measures that did not fully distinguish between sympathetic and parasympathetic involvement. For instance, several authors reported delayed or incomplete recovery of blood pressure or heart rate (Hassinger et al., 1999b; Holm, Lamberty, et al., 1997; Morley, 1985). More specific evidence of differences between migraineurs and controls in SNS recovery comes from studies using

vascular, electrodermal, and impedance measures, and these indices have typically suggested sustained sympathetic elevations following stressor offset in migraine sufferers (Gannon et al., 1981; Hassinger et al., 1999b; Huss et al., 2009; Leistad et al., 2008; Leistad, Stovner, et al., 2007).

However, group differences in autonomic recovery between migraineurs and controls are not universally reported in the literature. A handful of studies have produced reports of null findings on indices of both SNS and PNS during post-stress relaxation (Kröner-Herwig et al., 1988). When taking into consideration the methodological differences between these studies and those that report significant group differences between migraineurs and controls, the former tended to use more subtle and less effortful stressor manipulations, such as asking their participants to engage in mental imagery or exposing them to mild social discomfort by telling them they are being watched by others (Kröner-Herwig et al., 1988). In contrast, studies that found evidence of impaired recovery in migraineurs were more likely to have used more challenging or achievement-oriented stressor tasks, such as mental or visual arithmetic or speech presentation (e.g., Holm, Lamberty, et al., 1997).

1.1.4.3 Habituation. Using cardiac and electrodermal measures, several groups have reported impaired habituation to auditory, visual, and tactile stimuli in migraineurs (Ambrosini & Schoenen, 2003; Ellertsen & Hammerborg, 1982; Ozkul & Ay, 2007); however, some studies have failed to find this effect using sensory stimuli alone (Bäcker et al., 2001; Huber et al., 2005). Autonomic habituation to more complex stressors has been studied by a few authors. Huber et al. (2005) exposed participants to an achievement stressor (i.e., mental arithmetic with time pressure) and reported impaired habituation in migraineurs relative to control in both heart rate response and skin conductance. However, other studies using more sustained and mild

cognitive stressors that lasted more than 30 minutes (Kröner-Herwig et al., 1993; Leistad, Sand, Nilsen, Westgaard, & Stovner, 2007) found no difference between migraineurs and controls on measures of cardiovascular adaptation. It is interesting that, as in studies of reactivity to a single stimulus, these studies did find significant group differences in patterns of peripheral vasomotor activity (Kröner-Herwig et al., 1993). However, again, the direction of group effects differed from study to study.

1.1.4.4 The need for more research on autonomic recovery and habituation. The extant literature on the stress-migraine connection provides preliminary support for the importance of impaired habituation and recovery; however, previous studies of autonomic stress responses in migraineurs have important methodological constraints that make them poorly suited for the investigation of these two processes. First, the majority of laboratory stress studies examining stress recovery in migraineurs have used non-specific measures of autonomic arousal, such as heart rate or blood pressure. Such measures fail to differentiate between the relative contribution of sympathetic and parasympathetic branches in the ANS. Given their opposing but sometimes independent influences on more general indices of so-called "arousal," prolonged or incomplete autonomic recovery reflect sustained sympathetic hyper-arousal, diminished parasympathetic function, or both. Second, most of the studies of autonomic stress responses in migraine have examined reactivity to and recovery from a single stressor. In contrast, repeated intermittent stressors may be more relevant to the type of psychological stress that people encounter and that trigger migraines in daily life (Martin & MacLeod, 2009). However, the type of repeated stressor paradigm necessary to explore this possibility has not been applied in this population.

Several of the studies that have examined reactivity to and recovery from individual laboratory stressors have collected their data in a similar format to the way we plan to collect in

this study. A number of researchers have been interested in assessing group differences between migraineurs and controls on different types of stressors and have presented them to their participants intermittently on the day of laboratory testing (Cohen et al., 1983; Domingues et al., 2010; Hassinger et al., 1999b; Holm, Lamberty, et al., 1997; Kröner-Herwig et al., 1993). For instance, Hassinger et al. (1999b) examined responses to a cognitive stressor and a pain stressor; these two tasks were completed one after the other, with recovery to the first stressor serving as an adaptation period before the second stressor. However, results were analyzed and presented separately for each stressor task, and the order of stressors was counterbalanced for participants, thereby obscuring the possible effects of task order and repeated stressor exposure.

1.1.4.5 Prolonged ANS reactivity as a potential mechanism in subsequent migraine attacks. While mechanisms of the stress-to-headache sequence are only partially understood, contributions from the neuroscience literature suggest multiple possibilities for how this might occur (for a review, see Sauro & Becker, 2009). For example, autonomic hyperreactivity to stress could lead to subsequent headaches by amplifying central pain signaling and sensitizing peripheral nociceptors. The inability to return to lower/baseline levels of SNS activity could contribute to the development of migraine in several ways. The most notable way would be through mechanisms related to SNS hyperactivity.

Sustained SNS activity has been associated with an increased risk for developing headaches (Gass & Glaros, 2013), while pharmacological and psychological factors that decrease SNS activity tend to produce improvement in headache disorders (Nash & Thebarge, 2006). In addition, other common migraine triggers, such as sleep deprivation and alcohol, have been shown to produce increases in SNS activity (Dettoni et al., 2012; Van De Borne, Mark, Montano, Mion, & Somers, 1997; Zhong et al., 2005). Theoretical models propose that sustained activation

of the SNS contributes to simultaneous activation of the HPA axis. Both directly and through HPA mechanisms, sustained SNS activity stimulates the secretion of several neurotransmitters, including histamine, serotonin, noradrenaline and adrenaline in the brain and the secretion of adrenaline and noradrenaline into the blood stream. All of these result in subsequent activation of second messenger cascades, opening of ion channels and lowering of action potential threshold in the pathways of nociception (Taiwo, Bjerknes, Goetzl, & Levine, 1989).

Sensitization from this process seems to occur centrally by way of trigeminovascular neurons in the spinal trigeminal nucleus, which then projects to limbic areas and homeostatic nuclei (Burstein & Jakubowski, 2005). Peripherally, adrenaline and noradrenaline released from the adrenal medulla may act by binding to peripheral nociceptors and thereby reducing their threshold of firing (Taiwo et al., 1989). Sustained SNS arousal can also act on the locus coeruleus, which is capable of triggering CRH release from the hypothalamus (Jansen, Van Nguyen, Karpitskiy, Mettenleiter, & Loewy, 1995). Resulting stimulation of CRH receptors on the trigeminal nerve leads to extracranial mast cell degranulation (Theoharides, Donelan, Kandere-Grzybowska, & Konstantinidou, 2005). This secondary immune-related process results in release of vasoactive and inflammatory neuropeptides that increase vascular permeability and contribute to the pathogenesis of migraines (Theoharides et al., 2005).

Sustained abnormalities in the sympathetic and parasympathetic branches could lower the threshold for a subsequent migraine attack through distinct mechanisms and thus, will be examined separately in the current study. For example, the previously described sensitization of peripheral nerves to incoming sensory information—both directly and through the stimulation of pro-inflammatory immune responses—is more clearly linked to sustained elevations in the SNS. In addition, given the role of the PNS in returning the body to a more restful and restorative state,

failure to flexibly activate the PNS in the absence of an acute stressor could prevent appropriate behavioral and physiological withdrawal from additional stimuli that could trigger an attack. The continued sensory and emotional stimulation resulting from this "failure to withdraw" could result in additional irritation to sensory pathways that are already sensitized in migraine-prone individuals.

Finally, and perhaps most relevant to the present study, a phenomenon has been described in the clinical migraine literature: sustained stress followed by relaxation and perceived stress reduction may be the most common temporal sequence of events by which stress leads to migraine headaches (Goadsby, 2014; Holm, Lokken, et al., 1997; Lipton et al., 2014). This has caused some authors to suggest that the transition from a period of sympathetic hyper-arousal to a period of parasympathetic dominance and low arousal is a key biological mechanism linking stress to migraine attacks. Sustained elevations in SNS arousal followed by an exaggerated "rebound" in PNS tone could potentially explain how stress may lead to headache pain and numerous other symptoms occurring prior to and during the migraine attack itself. Such an autonomic "rebound" model of migraine pathogenesis could combine the previously described effects of sustained SNS elevation and initial parasympathetic suppression with the known behavioral and vascular effects of subsequent exaggerated PNS rebound; in this way, central and peripheral sensitization compounded by exposure to additional behavioral triggers would result in a lowered threshold for nociception, making migraineurs more susceptible to subsequent parasympathetically-mediated changes.

1.1.5 Stress-Related Cognitive Variables

Several psychological variables have been shown to modulate the physiological stress response by affecting the way that stressor-related information is processed. A few of these variables may

be particularly relevant in explaining patterns of sustained physiological hypervigilance in migraineurs.

1.1.5.1 Stress appraisal. Stress appraisal has received considerable attention as a cognitive variable that may directly affect physiological reactivity patterns. Based on the cognitive-appraisal model of stress (Lazarus & Folkman, 1984), two types of appraisals are made in the face of a stressor: the primary appraisal is an evaluation of the stressor itself—for instance, how threatening or challenging it is perceived to be—and the secondary appraisal, which refers to an individual's evaluation of his or her ability to cope with the stressor. Together, they can have a significant causal effect on an individual's emotional, behavioral, and physiological response to stress. While cognitive appraisal has more often been studied as a predictor of acute stress reactivity, appraisal during stressor exposure can also affect post-stress recovery (Haynes, Gannon, Orimoto, O'Brien, & Brandt, 1991)

In migraineurs, stress appraisal and subsequent coping have been shown to mediate the temporal relationship between daily stressors and subsequent migraines (Sorbi & Tellegen, 1988). There is also some evidence that migraineurs show more maladaptive patterns of appraisal than non-migraineurs. Several studies using questionnaires or daily-diary methodologies have found that migraineurs are more likely than controls to appraise stressful situations as negative or threatening, and to view themselves as less capable of handling stressors (Chiros & O'Brien, 2011; Ehde & Holm, 1992; Materazzo, Cathcart, & Pritchard, 2000; Sorbi & Tellegen, 1988).

However, this pattern of more negative stress appraisals in migraineurs has not always been supported. Hassinger et al. (1999a), for example, found that, when asked to evaluate the specific cognitive stressor task that they were completing in the laboratory, migraineurs did not

make more negative appraisals than controls. Thus, distinctions between trait and state stress appraisal may be important when attempting to classify abnormal appraisal patterns in migraineurs. Furthermore, no known research has examined whether individual differences in appraisal can explain the difficulties recovering from and habituating to stress that have been observed in these migraineurs.

1.1.5.2 Perseverative cognition. The construct of perseverative cognition includes several patterns of repetitive thinking—most notably worry and rumination—that are characterized by persistent cognitive processing of negative information, often in the absence of environmental demands for this processing (Brosschot, Gerin, & Thayer, 2006). Rumination has specifically been described as involving sustained attention to and elaboration on attentional focus on one's own negative mood (i.e., sadness, anxiety, anger), as well as the causes and consequences of that mood (Nolen-Hoeksema & Morrow, 1991).

In relation to the physiological stress response, engaging in one or more forms of perseverative cognition can prolong physiological stress responses to negative events (Gerin, Davidson, Christenfeld, Goyal, & Schwartz, 2006), and may sensitize some individuals to the types of stressors they are perseverating about (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). Worry is similar to rumination but involves less of a focus on personal feelings and previous events, and more of a focus on some problem or issue whose future outcome is uncertain (Brosschot et al., 2006). In the anxiety disorder literature, worry has been repeatedly linked to prolonged arousal and autonomic inflexibility (Brosschot, Van Dijk, & Thayer, 2007). Thus, engaging in perseverative cognition may bear particular relevance to patterns of impaired autonomic recovery, such as those reported in some migraine samples.

1.2 THE PRESENT STUDY

The present study aimed to characterize patterns of autonomic recovery and habituation to a repeated stressor in migraineurs, and to examine the role of key stress-related psychological variables (e.g., appraisal and perseverative cognition) in these patterns. The primary aims were focused on examining group differences between migraineurs and non-migraineurs on specific sympathetic and parasympathetic indices during a cognitive stressor paradigm.

Female undergraduates are in many ways an ideal population from which to recruit for this study. First, there is a surprisingly high prevalence rate of episodic migraine in young adult females (e.g., ages 18-29). Prevalence estimates depend on headache frequency criteria, but somewhere between 8 and 15% of this population have experienced symptoms in the past 6 months that would qualify them for a diagnosis of migraine. (Linet, Stewart, Celentano, Ziegler, & Sprecher, 1989; Stewart, Lipton, Celentano, & Reed, 1992). In addition, given their young age, and probable onset of migraines within the past few years, the majority of college females with episodic migraines have not yet progressed to more chronic, debilitating headaches. By that time, many have learned how to manage their headaches, identify triggers, and—for the purposes of this study—accurately self-identify their symptoms and patterns. Finally, the use of a relatively young and healthy sample of episodic migraineurs allowed us to avoid some of the theoretical and methodological concerns that arise when conducting research in more chronically ill participants (i.e., difficulty identifying discrete triggers, medication usage, neurobiological changes associated with chronic exposure to pain, etc.)

In order to explore potential group differences in these variables, the protocol used in the present study exposed participants to three separate periods of a cognitive stressor (e.g., Incongruent Stroop blocks) separated by brief periods of a relatively less challenging task (e.g.,

Congruent Stroop blocks). A unique feature of this study design was the use of a repeated intermittent stressor task that allowed for the simultaneous examination of both recovery following multiple stressors and habituation patterns in response to a repeated stressor. This task design was selected, in part, to simulate the nature of real-world stressors more accurately than other paradigms used to study reactions to multiple stressors—over the course of an average day, most individuals are not given opportunities for full "recovery" periods in between periods of high stress or challenge. Rather, most adults are exposed to periods of *relatively* less stress during which they must nevertheless remain engaged in the task at hand. Providing these relatively less challenging task blocks to participants in between the actual intended "stressor" periods also served the purpose of minimizing task disengagement (i.e., "giving up"), given the very challenging nature of the Incongruent Stroop task periods (described in greater detail below). Thus, the thrice-repeated stressor task used in the present study allowed for the possibility of group differences between migraineurs and controls in the ability to adapt (i.e., habituate) appropriately during stress re-exposure *and* the ability to recover following multiple stressor re-exposure with no opportunity for complete "recovery" in between these stressor blocks.

Based on these inconsistent prior results for acute stress reactivity, we posited that migraineurs and non-migraineurs differ from non-headache controls specifically in their ability to appropriately decrease autonomic arousal over time. We expected this pattern to manifest in several possible ways. First, we expected migraineurs' sympathetic responses to persist for longer or remain more elevated after a stressor concludes. Second, we expected migraineurs' sympathetic responses would have less habituation (e.g., adaptive decrease) to multiple presentations of the same stressor over time. Third, and alternately, we considered the possibility

that the re-initiation of parasympathetic function after stressor cessation could be blunted in migraineurs relative to controls; in other words, we expected that if differences were to occur between migraineurs and controls, they would be in the form of diminished vagal rebound. All three of this processes could lower the threshold for migraine onset through a variety of neurological, hormonal, or behavioral mechanisms.

For the autonomic outcome variables of the present study, indices of autonomic activity were derived from analysis of electrocardiogram (ECG), impedance cardiography (ICG), and electrodermal (EDA) measures. This was one of the first studies in the migraine stress literature to examine sympathetic and parasympathetic influences independently in the context of post-stress recovery. In contrast, habituation was examined using only sympathetic measures, as this construct mapped easily onto excitatory systems like the SNS, while the role of the PNS in habituation is ambiguous. Specific sympathetic measures included pre-ejection period (PEP) and skin conductance level (SCL), while the parasympathetic measure of interest was high frequency heart rate variability (HF-HRV).

In addition, in an effort to take into account cognitive factors that might foster prolonged and/or inflexible physiological responses, the present study also assessed individual differences in stress appraisal and perseverative cognition. Trait measures included one measure of appraisal and two different measures of perseverative cognition (worry and rumination). While these trait variables have been shown to correlate with laboratory stress responses, state measures tend to more closely predict physiological reactivity to a specific stressor. Thus, the present study made use of state measures of appraisal and perseverative cognition as well.

We hypothesized that migraineurs would report higher levels of perseverative cognition, and that observed differences in autonomic recovery between migraineurs and non-migraineurs

would be explained by individual differences in perseverative cognition. In addition, we hypothesized that cognitive stress appraisals would moderate the relationship between migraine group and autonomic habituation outcome variables.

We also examined several demographic and health-related variables to determine their usefulness as potential covariates, or even as explanatory variables in the stress-migraine association. Given their associations with alterations in physiological stress responses, we assessed the following variables: Age (Matthews & Stoney, 1988), BMI (Neumann, Sollers, Thayer, & Waldstein, 2004), and socioeconomic status (SES; McEwen & Gianaros, 2010), which have all been associated with alterations in autonomic stress reactivity. More proximal health-related variables, such as sleep (Franzen et al., 2011) and caffeine intake (Haynes et al., 1991), can also exert an effect on assessments of stress reactivity and recovery and will be collected in the current study.

Of note, many of these variables have also been associated with migraine development and progression (Houle & Nash, 2008; Katsarava et al., 2012; Nash & Thebarge, 2006); however, there is little research examining associations of these variables with migraine or migraineurs' responses to stress in younger and less impaired samples. Finally, some specific types of psychopathology that frequently co-occur with episodic or chronic migraine have also been linked to abnormal sympathetic and parasympathetic function at rest and in response to stressors, including depression (Taylor et al., 2006), anxiety (Merikangas, Angst, & Isler, 1990), and bipolar disorder (Nancy, du Fort, & Cervantes, 2003).

1.3 SPECIFIC AIMS & HYPOTHESES

1.3.1 Primary Aims

This study investigated two primary aims related to group differences in autonomic recovery and habituation. The first aim will examine group differences in autonomic recovery from repeated stress among migraineurs and healthy controls, using separate measures of sympathetic and parasympathetic function. Specific sympathetic measures include pre-ejection period (PEP) and skin conductance level (SCL), while the parasympathetic measure is high frequency heart rate variability (HF-HRV). The two hypotheses that I will explore for this aim include:

- Hypothesis 1a*:* Migraineurs will show decreased sympathetic recovery during the post-stress recovery period, as indexed by smaller reductions in sympathetic arousal relative to controls.
- Hypothesis 1b: Migraineurs will show decreased parasympathetic recovery during the post-stress recovery period, as indexed by reduced parasympathetic rebound relative to controls.

The second primary aim of the current study is to examine group differences in autonomic habituation to repeated intermittent stress in migraineurs relative to controls, using measures of sympathetic function. Habituation has historically been found in excitatory systems like the sympathetic nervous system (SNS); thus, for this aim, the present study focused on changes in PEP- and SCL-indexed arousal with repeated stress; however, habituation-like changes in HF-HRV were examined in an exploratory manner.

Thus, the following hypothesis will be explored.

- Hypothesis 2. Migraineurs will show decreased habituation to a repeated stressor, as indexed by smaller decreases in sympathetic arousal across multiple presentations of a repeated stressor relative to controls.

1.3.2 Secondary Aims

Our secondary aims relate to two stress-related cognitive variables that could help explain sustained physiological stress responses in migraineurs: perseverative cognition and stress appraisal. We examined these variables using both trait (i.e., dispositional) and state (i.e., situation-specific) measures of each of these variables.

Regarding the first secondary aim, perseverative cognition, no known studies have examined the extent to which migraineurs are prone to engaging in such perseverative thinking (e.g., rumination and worry). Given observed patterns of slower physiological and psychological recovery from stress in migraineurs, and the association of these variables with rumination and worry, it was hypothesized that:

- Hypothesis Secondary Aim (SA)1a. Migraineurs will report generally higher levels of trait perseverative cognition (e.g., worry and rumination) than controls.
- Hypothesis SA1b**.** Migraineurs will report higher levels of state (e.g., situation-specific) perseverative cognition than controls during the post-stress recovery period.

The next secondary aim is to relate cognitive and physiological mechanisms in autonomic recovery and habituation**.** With this aim, we sought to build upon findings of impaired autonomic responses by examining whether stress-related cognitive variables could help explain associations between these responses and migraine status, which results in four hypotheses:

- Hypothesis SA2a. Trait stress appraisal will moderate the relationship between migraine status and habituation, such that more negative trait appraisals will be associated with smaller reductions in sympathetic reactivity to a repeated stressor in migraineurs but not in controls.
- Hypothesis SA2b. State stress appraisal will moderate the relationship between migraine status and autonomic habituation, such that more negative state appraisals will be associated with a smaller reduction in sympathetic reactivity to a repeated stressor in migraineurs but not in controls.
- Hypothesis SA2c. Group differences in autonomic recovery will be explained by individual differences in trait perseverative cognition, such that migraine status will no longer predict significant variance in recovery variables when individual differences in trait worry and rumination are accounted for.
- Hypothesis SA2d. Group differences in autonomic recovery will be explained by individual differences in state perseverative cognition, such that migraine status will no longer predict significant variance in recovery variables when individual differences in state perseverative cognition are accounted for.

2.0 METHODS

2.1 PARTICIPANTS

2.1.1 Recruitment

For the purposes of the present study, we recruited individuals who met criteria for episodic migraine (henceforth these individuals will be referred to as the MI group), as well as a group of healthy control participants (henceforth the HC group). Based on power analyses for the primary hypotheses, we planned to recruit a conservative total of 68 female participants (34 participants per group).

Participants were recruited from a screening of Introductory Psychology students enrolled in the University of Pittsburgh's Psychology Department Research Pool. Students were given access to an initial online health screening questionnaire in order to identify individuals who reported experiencing migraine symptoms. In addition, this screening questionnaire also helped identify a candidate group of HCs who reported no migraines and very low-frequency headaches. To minimize effects of the menstrual cycle on stress responses (Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999), all participants were asked to report the date of their last menstrual period, and based on this information, assessments were scheduled during the follicular phase of each patient's menstrual cycle.

In order to confirm eligibility and ensure that all potential participants adhered to inclusion criteria, all individuals who passed the online screen as either MI or HC participants

were required to complete a phone screen containing questions about the inclusion/exclusion criteria noted below. As part of this phone screen, potential MI group participants completed a more detailed diagnostic screening to confirm information related to headache frequency and severity of symptoms.

For potential MI group participants, an initial diagnosis of migraine headache was established from online screening questionnaire responses using items from a 9-question structured interview designed to evaluate primary care patients based on the criteria for diagnosis of migraine established by the International Headache Society (Lipton et al., 2003). Importantly, this screening instrument included three items (assessing disability, nausea, and photophobia) that have demonstrated sensitivity and specificity to migraine headaches in a diverse primary care population and differentiated migraineurs from controls who experience tension-type headaches or other subtypes of headaches (Lipton, Bigal, Amatniek, & Stewart, 2004). Responses to these items were subsequently confirmed as part of the phone screen process.

In order to be included in the study, MI participants had to meet criteria for migraine without aura (MO) as defined by ICHD-2 criteria. The rationale for excluding individuals who suffer from migraine with aura (MA) was as follows: There is increasing evidence that MA and MO may be caused and maintained by at least partially differentiable biological mechanisms (Katsarava et al., 2012). Approximately 90% of individuals with MO report having identifiable triggers for their migraine attacks, while only 61% of MA patients do (Kelman, 2007). Most importantly, MO is more common in the general population and makes up the majority of individuals diagnosed with episodic migraine (Kelman, 2007), making this demographic the easiest subgroup to recruit for this study.

In accordance with the definition of episodic migraine, MI participants had to have experienced less than 15 headache days per month for at least the past three months. The rationale for recruiting episodic migraineurs and not chronic migraineurs is theoretical as well as practical: Stressors can be conceptualized as phasic triggers that—depending on the nature of the stress response—may lower the threshold of susceptibility for migraines; however, when migraine attacks become more frequent, as in chronic migraine, it becomes more difficult to identify individual triggers for headaches. Furthermore, the increased frequency and severity of headaches produces greater functional impairment and may prompt secondary changes in biological systems that process pain- and stress-related cues. For chronic migraineurs, the headaches themselves are also more likely to serve as primary stressors. In addition, only about 8% of migraine sufferers meet criteria for chronic migraine (Katsarava et al., 2012), which complicates both study recruitment and the generalizability of findings.

2.1.2 Additional Inclusion Criteria

Only female participants were chosen for this study to reduce variability in the physiological measures introduced by sex differences. In addition, all participants had to be between the ages of 18 and 45 and pre-menopausal, as hormonal changes associated with menopause are likely to have a substantial protective effect (MacGregor, Frith, Ellis, Aspinall, & Hackshaw, 2006). Exclusion criteria included use of prophylactic medication for migraine within 3 months of study enrollment, as many of these medications have either a direct or indirect effect on autonomic functions (Mills & Dimsdale, 1991). In addition, participants should not be taking medication for mood or anxiety disorders (e.g., beta-blockers, antidepressants, benzodiazepines), given their noted effects on SNS reactivity (Licht, Penninx, & de Geus, 2012). Additional exclusion criteria included lifetime diagnoses of hypertension or other cardiopulmonary disorders, a lifetime

diagnosis of neurological disorders (e.g., seizure disorders, multiple sclerosis, stroke). Control participants were required to meet the same exclusionary criteria as migraineurs.

As part of the phone screen, participants were informed that they should not have experienced a migraine headache in the three days prior to their assessment[1]. Participants were also asked to avoid drinking alcohol on the evening prior to the assessment, and participants who reported drinking 4 or more drinks on any one occasion within three days of the assessment (or reported drinking any alcohol the night before the assessment) were asked to contact the primary investigator (PI) to reschedule their assessment[2].

2.2 PROCEDURE

Upon participants' arrival in the lab, the study principal investigator and/or a trained research assistant confirmed that the subject had followed the instructions they had been given during the phone screen in preparation for the visit. Participants were given an initial explanation of the full study procedures. After completing the full consent procedure, participants' weight and height was measured and recorded. Participants were shown the physiological sensors that would be in use during the protocol and provided with instructions and a diagram for how to apply the torso ECG and impedance electrodes. For the purpose of privacy, research staff left the room while the participant undressed and applied the electrodes. Proper placement was checked upon staff re-entry, and preliminary psychophysiological recordings were taken to ensure a proper signal.

[1] Over the course of the study, two scheduled MI participants contacted the PI to request to reschedule their assessment due to recent or current/ongoing migraine attacks.

[2] Over the course of the study, four scheduled participants requested to reschedule their lab assessment appointments because of alcohol consumption.

Remaining electrodes and recording devices were applied. Participants were seated in a comfortable chair and the remaining recording equipment was secured. [3]

2.2.1 Stressor Protocol

Figure 1 provides a schematic representation of the experimental stressor protocol. After being seated, participants complete a brief initial questionnaire battery while preliminary physiological recordings were taken. State and trait questionnaires were presented at various points in the protocol as indicated in the figure. All questionnaires are described in greater detail below.

Participants were also asked to complete three standard visual analogue scale (VAS) ratings at indicated points during the protocol. For these brief assessments, they were asked to rate (on a scale of 1-5) how sad, happy, anxious, angry, frustrated, tired, bored, and stressed they felt at that moment. All questionnaires were completed by computer using the Qualtrics platform.

For the Baseline period, participants were asked to sit quietly and look at a red dot on the computer monitor for the duration of the 5-minute baseline. Immediately following the Baseline period and completion of the Task-Unrelated Thought (e.g., state perseverative cognition) questionnaire, participants were instructed on how to complete the Stroop task and were given an opportunity to complete two brief practice blocks. The task training served two purposes: 1) to allow participants to reach a base level of proficiency at the task, and 2) to provide participants with a brief exposure to the difficulty of the stressor in order to elicit subjective stress prior to task appraisal ratings. This training block was intentionally presented after the conclusion of the

[3] In addition to ECG, impedance cardiography, and skin conductance electrodes, participants were fitted with a breath belt and a mobile EEG unit, and were required to keep their chin in a chin rest while completing the protocol with simultaneous pupillometry recordings. Data from these measures was not included as part of the present study and are therefore not discussed further in this document.

baseline recording in order to avoid the possible effect of anticipatory anxiety on baseline measurements. A state measure of stress appraisal was collected after the training but prior to the beginning of the stressor protocol.

For the stressor task itself, participants completed a modified version of the Stroop color-word naming interference task, which is described in greater detail below. The stressor task was immediately followed by a 5-minute recovery period, during which participants were again asked to sit quietly and gaze at the red dot on the screen. Following the completion of the entire protocol, physiological recording equipment was removed and participants were asked to complete a final questionnaire battery containing trait and psychiatric symptom measures. Specific measures are discussed in greater detail below.

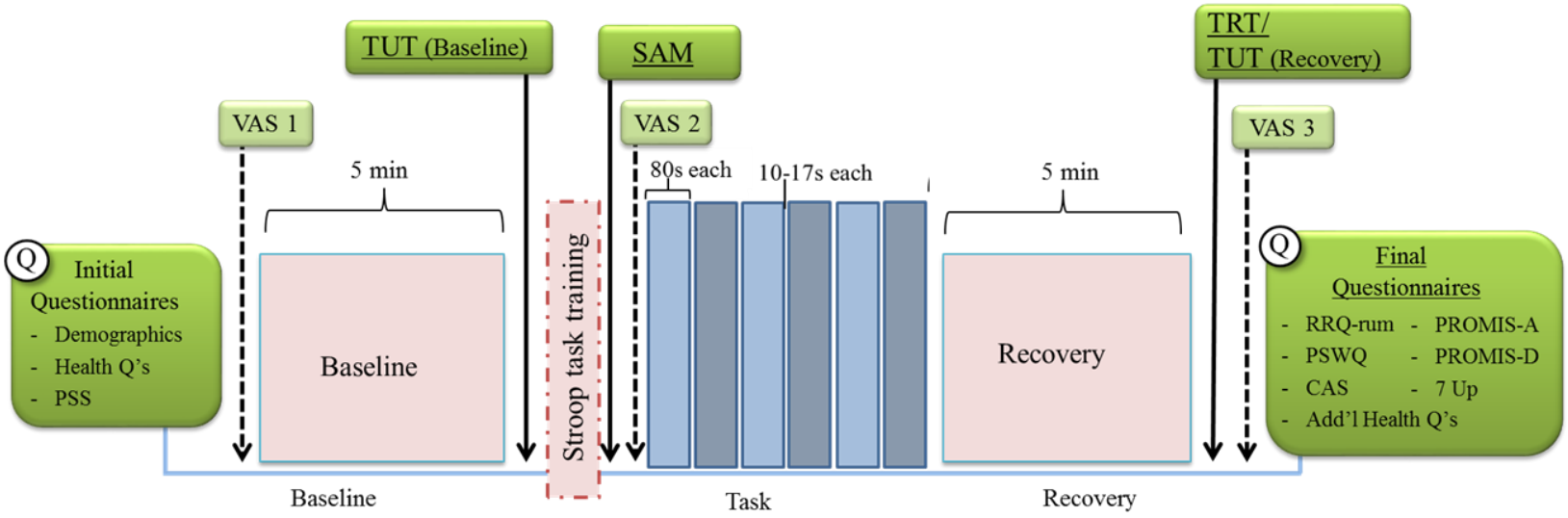

Figure 1. Experimental stress protocol: Modified Stroop task with pre-task baseline, post-task recovery, and self-report measures. PSS = Perceived stress scale; TUT = Task Unrelated Thought, and TRT = Task Related Thought (State questionnaire measures of perseverative cognition); SAM = Stress Appraisal Measure (State stress appraisal measure); RRQ-rum = Rumination Reflection Questionnaire—Rumination subscale and PSWQ = Penn State Worry Questionnaire (Trait questionnaire measures of perseverative cognition); CAS = Cognitive Appraisal Scale; PROMIS-A = PROMIS Anxiety Scale; PROMIS-D = PROMIS Depression Scale; 7 Up = 7 Up 7 Down Inventory - Mania symptom subscale

2.2.2 Stressor Task: Stroop Color-Word Interference Task

The Stroop task has been widely used as a psychological stressor in psychophysiological stress research because of its ability to provoke robust and reliable sympathetic responses (Fechir et al., 2008). Participants' laboratory responses to this task correlate well with their physiological responses to real life stressors (Kamarck, Schwartz, Janicki, Shiffman, & Raynor, 2003). The present study made use of a modified version of the Stroop task that was first described by Gianaros, May, Siegle, and Jennings (2005) in their neuroimaging study of cardiovascular reactivity. The task is divided into two conditions—an easier Congruent condition and more challenging Incongruent condition—both of which require participants to quickly identify the color of target words written on a computer screen over a series of trials. The color of the target word is identified by using a button press to select one out of four identifier words that correctly names the color of the target word.

On Congruent trials, the target word is written in a color that is congruent with the color that the target word names (i.e., "Green"), and all of the identifier words are written in the same color as the target word (i.e., "Yellow", "Red", "Green", "Blue"). For Incongruent trials, the target word is written in a color that is incongruent with the target word (i.e., "Green") and all of the identifier words are written in colors that are incongruent with the colors that the identifier words name (i.e., "Yellow", "Red", "Green", "Blue").

In the present study, several additional manipulations were included in order to make the Incongruent blocks considerably more challenging and/or threatening than Congruent blocks. One manipulation involved the addition of an auditory stimulus—a male voice naming a color. During Congruent blocks, the voice always named the correct color; however, during Incongruent blocks, color names were randomly presented, and thus the voice served as an

auditory distractor. In addition, during Incongruent blocks, participants were presented with a loud buzzer sound and negative visual feedback when they got an answer incorrect or they did not respond within the required time window as determined by the task program. To control for individual differences in task performance and perceived task difficulty, the timing of stimulus presentation was made to vary during the Incongruent condition, such that participants' word identification accuracy during each Incongruent block was maintained at approximately 60% accuracy. During the stressor protocol, participants completed six 80-second blocks of alternating Congruent and Incongruent trials. Each block was preceded by a 10- to 17-second rest period during which participants fixated on a crosshair.

2.3 PHYSIOLOGICAL MEASURES

The present study made use of two physiological indices of sympathetic arousal, one cardiac (pre-ejection period; PEP) and one electrodermal (skin conductance level; SCL). The rationale for using two measures was that participants could potentially provide information about independent components of the sympathetic response to mental stress.

While both PEP and SCL are considered to index sympathetic arousal and therefore, reflect increased mobilization of metabolic resources in order to respond to a stressor, they show little or no correlation between subjects or within a single subject across multiple laboratory stressors (Goedhart, Willemsen, & De Geus, 2008). This is particularly true for mental stress tasks in which the metabolic demands needed to respond appropriately to the stressor may vary more depending on contextual features and on the subjective experience of the stressor. Some authors have suggested that, relative to cardiac measures, electrodermal measures of arousal

more closely reflect defensive arousal responses adopted when an individual perceives that he or she is under threat (Tomaka, Blascovich, Kelsey, & Leitten, 1993). In contrast, cardiac measures of arousal like PEP are thought to be more sensitive to stressful situations that elicit behavioral approach, in which the individual feels challenged, energized, and eager to perform (Brenner, Beauchaine, & Sylvers, 2005; Tomaka et al., 1993). For the purpose of the preset study, it is unclear whether patterns of impaired recovery and habituation previously seen in migraine sufferers reflect one type of response versus the other. In addition to PEP and SCL, we used a third physiological measure of heart rate variability. All of these measures are described in more detail below.

2.3.1 Pre-Ejection Period

Pre-ejection period (PEP) is considered to be a relatively pure and reliable index of sympathetic activity obtained from electrocardiogram (ECG) and impedance cardiography (ICG) recordings (Berntson et al., 1994; Burleson et al., 2003). More specifically, PEP reflects beta-adrenergic influences on heart contractility, and it is quantified as the interval between the onset of ventricular depolarization and the onset of ventricular ejection. PEP is inversely related to the degree of sympathetic arousal; such that shorter PEP values correspond to greater sympathetic cardiac control.

2.3.2 Skin Conductance Level

Skin conductance level (SCL) is a straightforward measure of sympathetic sudomotor activity that has frequently been used in studies of emotional responses to threats and stressors (Jacobs et al., 1994). Fluctuations in skin conductance are a result of cholinergic influences on eccrine sweat glands. Relative to some other measures of electrodermal activity, SCL provides an index

of tonic electrodermal activity over longer time intervals (i.e., on the order of tens of seconds to minutes). Because raw skin conductance (SC) values can also fluctuate much more rapidly in response to specific threat stimuli, rapid phasic phenomena are often quantified separately as skin conductance responses (SCRs). Since the present study made use of an experimental block design and data epochs for mean sympathetic arousal were quantified in minutes, SCL was used to assess these relatively prolonged sympathetic responses.

2.3.3 High Frequency Heart Rate Variability

Heart rate variability (HRV) is a measure of the ongoing beat-to-beat variations in heart rate produced by the interplay of sympathetic and parasympathetic neural activity (Berntson et al., 1994). High frequency HRV (HF-HRV) is generally regarded as being completely under parasympathetic (i.e., cardiac vagal) control, and in healthy individuals, exposure to laboratory threat stimuli and stressor tasks like the Stroop have been shown to reliably induce a physiological state of arousal characterized by increased heart rate and simultaneously decreased HF-HRV (Hoshikawa & Yamamoto, 1997; Johnsen et al., 2003).

2.4 PHYSIOLOGICAL DATA COLLECTION AND CALCULATION

Autonomic measures were collected continuously for the duration of the baseline period, and from the beginning of the Stroop task to the end of the recovery period. Data were acquired on a Bionex-50 acquisition system (Mindware Technologies, Gahanna, OH). ECG and impedance cardiography (ICG) data were acquired via seven electrodes placed on the following body locations: the three ECG electrodes were placed below the right collar bone (4 cm from the sternum), at the inferior tip of the heart/over the ninth rib (left side of the chest), and on the right

abdomen between the lower two ribs; the two ICG current electrodes were placed on the back, directly over the spine at levels C4 and T8, while the two ICG measuring electrodes were placed at the top of the sternum and at the xiphisternal junction. SC was measured using two pre-gelled 1-1/2" foam electrodes placed on the middle segment of participants' third and fourth fingers. For this study, SC electrodes were the first to be attached, and were worn for the duration of remaining equipment setup and initial questionnaire period to allow for maximum electrode stabilization. All signals were sampled at a frequency of 1000 Hz.

PEP and HF-HRV values were both derived from continuous ECG recordings taken over the course of the baseline and stress protocol recording periods. Raw ECG data were corrected for artifacts and abnormal heartbeats were removed using MindWare HRV 3.1.3 software (MindWare Technologies, Ltd., Gahanna, OH). This program uses an automated R-wave detection algorithm that flags abnormal data, after which artifacts were removed manually using guidelines described by Berntson et al. (1997). (< 1% of all R-waves required correction.) Additional visual inspection was performed on all non-flagged data to ensure accuracy. The high frequency (HF) power component of HRV was calculated using the same MindWare program. Spectral analysis was conducted on interbeat interval (IBI) timeseries that had been de-trended, end tapered using a Hamming window, and subjected to a fast Fourier transform in order to isolate power values within the 0.15–0.50 Hz spectral range. Resulting HRV values were non-normally distributed and natural log transformations were applied to reduce skewness.

PEP values were calculated by ensemble-averaging ECG and dZ/dt signals using MindWare IMP 2.56 software (MindWare Technologies, Ltd., Gahanna, OH). ECG artifacts were previously dealt with as described above. Artifacts in the dZ/dt signal were removed and equivalent R-peaks were deleted from the ECG data when necessary (less than 1% of all data).

PEP was calculated as the time in milliseconds from the onset of the Q-wave in the ECG signal to the B-point of the dZ/dt signal, in following with (Berntson, Lozano, Chen, & Cacioppo, 2004). An automated algorithm was run first to provide a quantitative estimate of the B-point for instances in which the B-notch was not clearly visible (Lozano et al., 2007). Manual inspection and artifact removal was then conducted, and inaccurate landmark placement was corrected based on clear visual features of the waveform. Approximately 5% of data were edited.

For the present study, we used 10-second ensemble averages to compute raw PEP time series. The 10-second window was selected in order to generate a long-enough time series for each epoch of interest while maintaining reliable data. Reliability was established via correlations of mean values derived from 5-, 10-, 30-, and 60-second ensemble averages for the first 29 participants (12 HC, 17 MI). A cutoff of $r = .9$ was established. PEP values calculated from 10s averages were found to correlate significantly with PEP values calculated from longer ensemble averages (e.g., 30- and 60-seconds). While ensemble averages as short as 5 seconds have been shown to produce enough reliability to use, 10s averages were used in this study because they were the shortest periods shown to produce reliable values above the cutoff.

SCL values were derived from second-by-second time series for the length of each epoch of interest. Data were inspected and cleaned using MindWare EDA 3.0.25 software. Isolated movement artifacts were identified manually; where these were suspected, SCL data was compared with simultaneously-collected breath belt data to confirm movement. A cutoff of 20 μS was used to identify erroneous data, which were then excluded from analyses.

2.5 SELF-REPORT MEASURES

2.5.1 Trait Stress Appraisal

Trait patterns of cognitive appraisal were assessed using the Cognitive Appraisal Scale (CAS), an 18-item measure consisting of two nine-item subscales: the Threat subscale and the Challenge subscale. The Threat subscale assesses an individual's tendency to focus on perceived threats, one's performance, self-esteem, and social identity, accompanied by low self-confidence in one's own ability to cope with stressful situations (Cronbach's $\alpha = .78$ as reported by Ellsworth & Smith, 1988). The Challenge subscale assesses expectations of success and positive outcomes accompanied by high confidence in one's capacity to achieve these outcomes (Cronbach's $\alpha = .89$; Ellsworth & Smith, 1988; Lazarus, 1991; Lazarus & Folkman, 1984; Lazarus et al., 1980; Smith, 1991).; and 10 items referred to threat appraisals. Participants indicated on a scale of 1 (not at all) to 6 (very much) the extent to which each statement is true for them right now.

2.5.2 Trait Perseverative Cognition

2.5.2.1 Rumination. To assess trait rumination, participants completed the 12-item Rumination subscale of the Rumination Reflection Questionnaire (RRQ-R) (Trapnell & Campbell, 1999). The Rumination subscale assesses negative recurrent thoughts about the self, similar to earlier versions of depressive rumination measures (i.e., Trapnell & Campbell, 1999), but without reference to depressed mood. Items are rated on a five-point scale ranging from 1 = Strongly disagree to 5 = Strongly agree. Trapnell and Campbell (1999) reported the internal consistency coefficient estimates for the Rumination subscale as $\alpha = 0.90$.

2.5.2.2 Worry. To assess participants' habitual levels of worry, we administered the Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990). The PSWQ is a 16-

item questionnaire designed to measure the excessiveness, duration and uncontrollability of worry experienced by an individual. Participants rate items such as, “Once I start worrying, I cannot stop,” on a 5-point Likert scale (1 = Not at all typical of me, 5 = Very typical of me). The 16-item PSWQ displays a very high internal reliability ($\alpha = 0.94$).

2.5.3 State Stress Appraisal

To assess state stress appraisal, participants completed the Threat, Challenge, and Controllability (also called “Control by Self”) subscales of the Stress Appraisal Measure (SAM) (Peacock & Wong, 1990). The full SAM is a 28-item measure that assesses cognitive appraisals of stress using a 5-point Likert scale (1 = Not at all, 5 = Extremely). Currently, the SAM is the only measure of its kind with substantial theoretical and psychometric support for its validity. Based on cognitive appraisal theory (Lazarus & Folkman, 1984), the SAM assesses an individual’s general attitudes towards future situations. Items from the Threat subscale are designed to measure the potential harm/loss in a situation, whereas the Challenge subscale items primarily tap the potential for gain or growth. Estimates of internal consistency derived from three studies of college students ranged from .65 to .81 for the subscales. In the present studies, participants completed the SAM immediately after learning and practicing the stressor task for several trials, and before the task itself began.

2.5.4 State Perseverative Cognition

State perseverative cognition was measured using the Task Related Thought (TRT) and Task Unrelated Thoughts (TUT) sections from the longer Dundee Stress State Questionnaire. These two short questions are designed to be given in the context of a specific stressor task, and they assess two particular cognitive factors: perseverative concerns or preoccupation with task

performance (e.g., Task Related Thought), and general worry about things other than the task (e.g., Task Unrelated Thought). The scales are built on the construct of task-relevant and task-irrelevant cognitive interference, and in this way are an excellent state proxy for trait measures of intrusive, repetitive thought (e.g., worry or rumination).

In the present study, the TUT was given after both the baseline and recovery periods, while the TRT was given only after the recovery period. Although other studies in the literature have used thought-sampling techniques to measure processes like worry or ruminative thought over the course of an entire task, we placed these measures after rather than during epochs of interest in order to clean measures of the primary dependent variables (physiological stress recovery and habituation) without inducing changes related to answering the questionnaires. For both presentations of the TUT or TRT/TUT, participants were asked to reflect on the thoughts they had been having over the last five minutes (e.g., while they were looking at the dot).

2.5.5 Additional Measures

2.5.5.1 Basic demographic and health variables. Self-reported age, race, and SES measures were collected via standard demographic questionnaire. The present study utilized a composite measure of undergraduate SES based on self-reported parental education levels and perceived family income level (Donaldson, Lichtenstein, & Sheppard, 2008). This measure makes use of Likert scales to assess educational achievement (from 'Did not finish high school' to 'Completed a Doctoral or Professional degree [JD, MD, PhD, etc.]') and perceived income level (from 'Low income' to 'High income'), which appear to be more accurate and reliable than specific estimates of number of years of parents' education and family income in thousands of dollars. Body mass index (BMI) was determined using laboratory measures of height and weight taken the day of the assessment. BMI values are calculated as weight (in kilograms) divided by height (in meters)

squared. Current smoking status was measured via a single question asking whether or not participants were smokers. Participants were also asked to report on several *phasic* health variables occurring proximally to the lab assessment, including hours of sleep the previous night, caffeine intake, tobacco use, and medication use the day of the assessment. These variables were tested as possible covariates for primary analyses in this study.

2.5.5.2 Psychiatric symptom measures. Given the heightened prevalence of mood and anxiety disorders in migraineurs (Juang, Wang, Fuh, Lu, & Su, 2000), and associations of these disorders with changes in autonomic cardiac function (Bylsma, Salomon, Taylor-Clift, Morris, & Rottenberg, 2014; Pittig, Arch, Lam, & Craske, 2013), measures of current depression, anxiety, and mania-related symptoms were included in the self-report battery for this study. Depression and anxiety-related symptoms were assessed using two related item pools from the patient-reported outcomes measurement information system (PROMIS), developed for screening purposes by the National Institutes of Health (Cella et al., 2010). These item pools have been tested in a large sample of general population respondents, augmented by clinical samples, and item response theory (IRT) methodology was used to select and calibrate items for the PROMIS item banks (Pilkonis et al., 2011). In addition, self-reported symptoms of mania were assessed using the 7 Up subscale of the 7 Up 7 Down Inventory (Youngstrom, Murray, Johnson, & Findling, 2013). This Mania subscale contains 7 items assessing manic and hypomanic tendencies, and has been shown to have good internal consistency in college students.

2.5.5.3 Life stress. To assess the degree to which participants appraise their lives as stressful over the previous month, participants completed the Perceived Stress Scale (PSS) (Cohen, Kamarck, & Mermelstein, 1983) on the day of their laboratory assessment. The PSS is a 14-item scale designed to measure how unpredictable, uncontrollable, and overloaded respondents

perceive their lives to be. It was constructed to tap into four subdomains of perceived life stress: unpredictability, burden overload, lack of control, and stressful life circumstances. In college student samples, estimates of internal consistency have been reported as .84-.86, and test-retest reliability as .85.

2.5.5.4 Headache characteristics. Migraine participants were given an additional questionnaire assessing various aspects of their migraines, including headache frequency, history (e.g., age of onset, presence or absence of formal diagnosis), and typical migraine triggers. The questionnaire also assessed various symptoms and features of the migraines attacks themselves, in order to confirm diagnostic criteria originally assessed in the online screening process.

2.6 PHYSIOLOGICAL DATA REDUCTION AND DEPENDENT VARIABLE SPECIFICATION

Due to the observation that some measures needed longer to acclimate, baseline values for all three primary dependent variables were specified by taking an average of the last three minutes of the baseline recording period (henceforth referred to as Baseline). Values for preliminary examination of stress-related reactivity were derived by averaging SCL, PEP, and HRV values across each 80-second incongruent period, resulting in three separate task values for each participant (henceforth referred to as Incon1, Incon2, and Incon3). In line with existing standards, reactivity values for HRV were operationalized as vagal withdrawal, calculated by subtracting baseline values from each of the three incongruent blocks.

2.6.1 Sympathetic Recovery

For the two sympathetic indices (SCL and PEP), recovery values for each subject were quantified from continuous time series for the full five-minute recovery period. SCL time series consisted of second-by-second SC values, while PEP time series consisted of thirty consecutive 10s ensemble averages (rationale for and calculation of 10s ensemble averages are described above in Physiological data collection and processing). Due to the noisiness of the PEP data, a 10-kernal smoothing algorithm was applied to PEP recovery time series prior to fitting of a curve as described below.

To generate variables that accurately conveyed the full time course of recovery for each participant, a gamma function was calculated for each participant on each sympathetic variable (see Figure 2 for example plots). Each gamma function included three parameters: an offset parameter (referred to as the alpha [α] parameter), a rise-decay parameter (referred to as the beta [β] parameter), and a height parameter. The alpha parameter conveys how long it takes for the response to begin, while the beta parameter conveys the smoothness of the response. The height parameter roughly corresponds to the average magnitude of the variable across the recovery period time series. Thus, each participant had three SCL recovery values and three PEP recovery values. In the present sample, the α parameter for SCL and the β parameters for SCL and PEP were not normally distributed and were natural log-transformed prior to statistical analysis. The height parameter roughly corresponds to the average magnitude of response across the full time series. Thus, for analysis on sympathetic recovery, each participant had three SCL recovery values and three PEP recovery values.

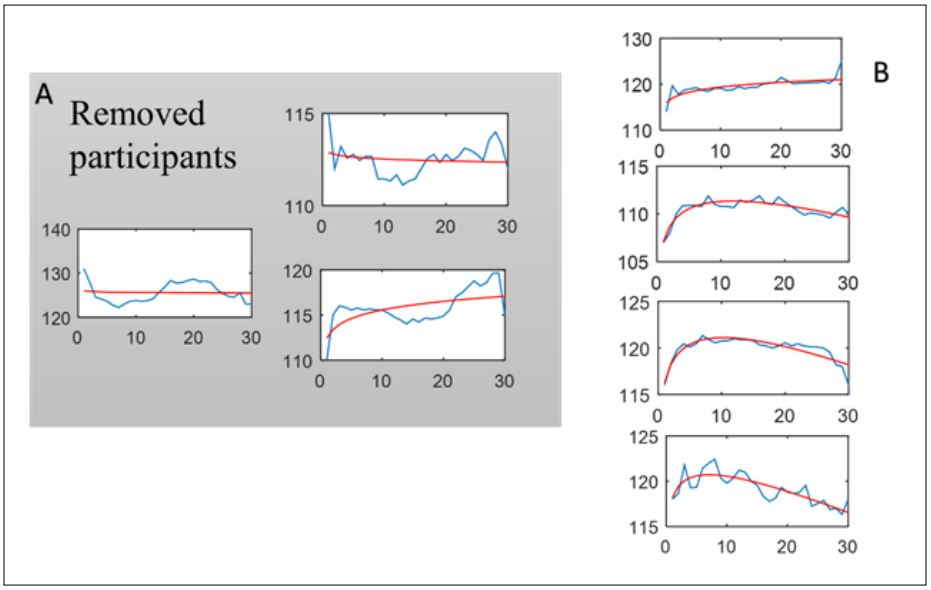

Figure 2. Sample plots created with gamma function parameters, overlaid on PEP recovery time series. 2A presents examples of data that were removed from PEP recovery analyses due to poor gamma fits and 2B presents examples of data used for final analyses.

To effectively deal with large datasets across multiple participants, this procedure was conducted in MATLAB and resulting gamma function parameters and fit statistics were exported for final statistical analysis in SPSS. Gamma fits were inspected visually as a graph was generated for each participant with the predictor line overlaid on observed recovery time series values for each variable. Quantitatively, gamma fit statistics (*R* and mean standard error [MSE]) were generated for each participant. Participants with an $r < .3$ or MSE > 2.5 were excluded from the analysis (see Figure 2 for visual examples of excluded datasets). This resulted in the removal of 7 participants from the SCL analyses (5 HC, 2 MI) and 6 participants from the PEP analyses (3 HC, 3 MI). See Table 1 for a list of unusable data for autonomic variables.

Table 1

Missing and Unusable Data on Primary Autonomic Measures

	Missing data			**Removed data**			**Total *N* (primary analyses)**			**Removed recovery data**			**Sympathetic recovery *N***		
	All	**HC**	**MI**	**All**	**HC**	**MI**	**All**	**HC**	**MI**	**All**	**HC**	**MI**	**All**	**HC**	**MI**
SCL	5	3	2	2	1	1	**65**	34	31	7	5	2	**58**	29	29
PEP	3	3	0	2	1	1	**67**	33	34	6	3	3	**61**	29	32
HRV	4	3	1	2	1	1	**66**	34	32	--	--	--	--	--	--

Note: HC=health control group; MI=migraine group; SCL=skin conductance level; PEP=pre-ejection period; HRV=(high frequency) heart rate variability.

2.6.2 Parasympathetic Recovery

For the present study, parasympathetic recovery was quantified as vagal rebound during the recovery period. Vagal rebound refers to a quick upsurge in parasympathetic tone immediately following stressor cessation. This "rebound" from the vagal withdrawal observed during stressor exposure appears to be responsible for the rapid heart rate deceleration observed in the first minute of recovery despite continued sympathetic activation (Mezzacappa, Kelsey, Katkin, & Sloan, 2001). Thus vagal rebound is thought to be essential in reestablishing homeostasis in the cardiovascular system following a stressor.

In research studies, vagal rebound is quantified as the extent to which HF-HRV increases after stressor cessation. While vagal rebound can be calculated in a variety of ways, in the present study a change score was calculated as described in (Mezzacappa et al., 2001), by subtracting the peak vagal withdrawal recorded during the stressor task (e.g., the lowest HRV value recorded across Incon 1, Incon 2, and Incon 3) from the mean of the first minute of recovery. For the purpose of the present study, this will henceforth be referred to as *peak vagal rebound*. An alternate vagal rebound value was also calculated by subtracting vagal withdrawal

on Incon 3 from the final minute of recovery, and this stressor epoch was proximally the closest to the recovery period. This will henceforth be referred to as *final vagal rebound*. Two vagal rebound scores were therefore calculated for each participant.

2.6.3 Sympathetic Habituation

For the present study, sympathetic (PEP and SCL) habituation to repeated stress was quantified as the extent to which sympathetic reactivity decreases across repeated presentations of a stressor (e.g., Incongruent blocks). We are aware that, from a physiological standpoint, the construct of habituation is far more complex and is controlled by a number of underlying physiological processes that differ depending on the system being studied. For the purpose of the present study, we were interested in the degree to which migraineurs might fail to appropriately reduce autonomic reactivity to repeated presentations of a stress stimulus. We operationalized habituation simply as the extent to which sympathetic arousal decreased (e.g., SCL values decreased, PEP values increased) across Incongruent blocks. As described below, primary analyses of habituation were performed on mean reactivity levels for each Incongruent block.

2.6.4 Exploratory Variable: Parasympathetic Habituation

Habituation of physiological responses has typically been measured in excitatory systems like the SNS—in contrast, the role of the PNS in this process is more ambiguous. In order to examine potential group difference between migraineurs and controls on “habituation-like” PNS changes with repeated stress (e.g., successive decreases in vagal withdrawal across repeated stressor blocks), we examined parasympathetic changes in an exploratory manner.

2.6.5 Additional Data Preparation

Autonomic data across all epochs were inspected for outliers; epochs with extreme outliers (> 3 SD from the mean) were removed from subsequent analyses (See Table 1 for a summary of missing or removed data). Epochs with outliers falling outside Tukey Hinges plus or minus 1.5*IQR were replaced with Tukey Hinges plus or minus 1.5*IQR. Two participants' (both in HC group were removed due to extreme HRV and PEP data values on all epochs. For HRV data, one lower outlier was rescaled for a single epoch (minute 1 of recovery) for one participant (MI; rescaled ~3.1 to 3.4). One lower outlier was rescaled for a single epoch for 1 participant (HC) on PEP response, (rescaled ~95 to ~98), while two upper outliers were rescaled (2 MI; rescaled ~139 and ~136 to ~131). Upper outliers were rescaled (rescaled ~ 30 to ~20) for a single epoch for 2 participants (1 HC, 2 MI) on SCL. Any residual outliers for specific analyses found are discussed in the relevant sub-section of the Results section.

A total of 75 participants completed the full study protocol, however 3 participants' data were excluded from the dataset immediately due to violations of study inclusion criteria: two participants (1 HC, 1 MI) reported via questionnaire that they had taken stimulant medication on the day of the assessment, and one HC participant disclosed after the experiment that she had a history of a benign brain tumor accompanied by severe headaches that had been surgically removed. Thus, these participants' demographic, self-report, and behavioral data were also excluded from remaining analyses. Of the remaining 72 participants, physiological data were lost due to equipment problems for 5 participants' SCL responses, 3 participants' PEP responses, and 4 participants' HRV responses. Cases of missing or excluded data and final participant counts on each autonomic dependent variable are listed in Table 1.

2.7 STATISTICAL ANALYSES

All physiological and self-report data were inspected for deviations from normality. Variables with non-normal distributions were subjected to suitable transformations when appropriate for the analyses used (e.g., log transformations on HRV data as described above). Variables that were not amenable to transformation (e.g., participant age) were subjected to non-parametric tests.

2.7.1 Preliminary Analyses

Means and standard deviations were calculated for age, composite SES, BMI, sleep (in hours), perceived stress, perceived life stress, and psychiatric symptom measures. Frequencies were calculated for race, and dichotomized SES variables. Means and standard deviations were also calculated for percent (%) correct responses for each Stroop stressor period, as well as VAS ratings for relevant emotion words collected at Baseline, immediately pre-stressor, and following the Recovery period. Harmonic means of reaction times were calculated within subjects for each condition.

For behavioral and self-report variables, outliers falling outside Tukey Hinges plus or minus 1.5*IQR were replaced with Tukey Hinges plus or minus 1.5*IQR. Within self-report measures, two upper outliers were corrected for the PSS (both MI), and one lower outlier was corrected for the RRQ (MI). In addition, for state appraisal and perseverative cognition measures, two upper outliers were corrected for SAM Threat (1 HC, 1 MI), one upper outlier was corrected for post-task TRT (MI), and two upper outliers were corrected for the post-task TUT questionnaire (both HC).

The primary hypotheses for this study focused on recovery and/or habituation of autonomic responses. The extant literature has failed to show systematic differences between migraineurs and controls on baseline measures of autonomic function or in acute stress-related reactivity levels; thus, we expected to find few if any group differences in baseline reactivity or reactivity for these variables in the present sample. However, if such differences should occur, we wanted to make sure that they would not fully explain any observed group differences in recovery or habituation.

Thus, for preliminary physiological analyses, independent samples *t*-tests were used to test for group differences in baseline autonomic function for all three primary physiological measure (SCL, PEP, and HRV). To test reactivity, a set of 2 (Group: MI vs. HC) x 4 (Period: Baseline, Incon1, Incon2, Incon3) repeated measures ANOVAs were run for each variable. Main effects of Period were examined to confirm the presence of stressor-evoked changes across the sample. Univariate tests were used to follow up significant multivariate effects of Period to ensure that the physiological variables of interest appropriately increased (for SC) or decreased (for PEP and HRV) from baseline. Group x Period interactions were examined to determine whether migraineurs showed differential reactivity to stressor task blocks. For all repeated measures analyses, Mauchly's test of sphericity was used to identify heterogeneity of covariance, and results are presented with Greenhouse-Geisser[4] corrections for degrees of freedom where this assumption was violated; homogeneity of variances was tested using Levene's test for equality of variances; normality of residuals were assessed via Q-Q plot; Box's test was used to test homogeneity of covariance matrices. For all preliminary analyses of self-report and behavioral task variables, significance level was adjusted to correct for family-wise error rates.

[4] There were no instances in which making this adjustment resulted in a loss of otherwise significant results.

Analyses were conducted using a Bonferroni-corrected alpha that varied by family[5]. We did not apply additional corrections to preliminary group comparisons of the three primary dependent autonomic variables, as we regard this measures as independent and influencing potentially different mechanisms of stress-related migraines.[6]

2.7.2 Primary Aims: Group Differences in Autonomic Recovery and Habituation

The primary aims of the present study were to determine whether individuals with migraines differ from non-migraine controls in terms of their autonomic recovery and habituation in response to a repeated intermittent stressor. To test the hypothesis that migraineurs would show decreased *sympathetic* recovery during the post-stress recovery period, independent samples *t*-tests were used to test for group differences in gamma recovery parameters (α, β, and height, reflecting latency to recovery, rate of recovery, and magnitude of recovery, respectively) for each of the sympathetic measures (SCL, and PEP). Several of these variables had non-normal distributions that could not be effectively corrected using standard transformations; for group comparisons on these variables Mann-Whitney U tests were run in place of *t*-tests.

To test the hypothesis that migraineurs would show decreased parasympathetic recovery during the post-stress recovery period, independent samples *t*-tests were performed on vagal rebound values. As discussed in the section on Physiological data reduction and dependent variable specification, vagal rebound was calculated separately as peak and final vagal rebound values, resulting in a total of two *t*-tests for this hypothesis. Here, family-wise Type I error correction was applied to account for the test of two related means ($\alpha = .025$).

[5]Stroop RTs / %-accuracy: $\alpha = .05/2 = .025$; VAS emotion ratings $\alpha = .05/4 = .0125$;

To test the hypothesis that migraineurs would show decreased sympathetic habituation to a repeated stressor, separate 2 (Group: MI vs. HC) x 3 (Period: Incon1, Incon2, Incon3) repeated-measures ANCOVAs were performed on mean SCL and PEP values. To control for individual differences in baseline and initial reactivity, (e.g., Incon1-Baseline change scores) these variables were entered as covariates for each model. An analogous repeated measures ANCOVA was used for exploratory analyses investigating parasympathetic "habituation". Significant Group x Period interactions would be indicative of differential habituation between migraineurs and controls. For ANCOVA analyses, all the same tests of statistical assumptions were applied as for other repeated measures ANOVA, as well as visual inspection of standardized residuals plotted across predicted values to assess for homoscedasticity.

2.7.3 Secondary Aims: Stress-Related Cognitive Variables

To test for group differences in the trait (i.e.., worry and rumination) and state perseverative cognition (e.g., task-related and task-unrelated thought), separate independent-samples *t*-tests were conducted to compare means for the MI and HC groups on these variables. In response to advice from committee members, a pre-task measure of task-unrelated thought was added in order to determine whether any state differences post-task existed prior to the task as well.

Secondary aim 2 centered on two sets of analyses. The first set were intended to test whether state and trait stress appraisal would moderate the relationship between migraine status (e.g., Group) and measures of sympathetic habituation. The second set of analyses were intended to test whether any observed group differences in autonomic recovery would be explained by individual differences in perseverative cognition.

To determine whether trait and state stress appraisals (threat and challenge) moderate associations between migraine status and rates of habituation, separate 2-step hierarchical

regressions were conducted for relevant state and trait appraisal variables. For each regression, Group and (Trait or State) Appraisal were entered together at step 1, and a Group x Appraisal interaction term was entered at step 2. If appraisal was indeed a moderator, the inclusion of the interaction term would result in a significant increase in variance explained at step 2. For these analyses, habituation (the DV) was quantified as the slope of change in reactivity across Incongruent blocks.

To explore different dimensions of trait stress appraisal, separate analyses were run examining threat appraisals (i.e., negative appraisals) and challenge appraisals. As discussed previously, threat and challenge appraisals have been shown by some research to be differentially associated with different physiological outcome measures (e.g., Tomaka et al., 1993). As such, four separate regressions were run to test for trait appraisal as a moderator (two regressions for two sympathetic measures). For state appraisal analyses, this hypothesis only concerned negative (i.e., "threat") appraisals, and thus only two regression analyses were run for this hypothesis (one for each sympathetic measure).

To determine whether any observed group differences in autonomic recovery could be explained by individual differences in trait or state perseverative cognition, additional hierarchical regression analyses were to be used to test whether migraine status continued to explain significant variance in recovery after accounting for individual differences in trait and state perseverative cognition. These analyses would only be performed on relevant recovery variables (e.g., sympathetic gamma function parameters and/or parasympathetic [vagal] rebound values) that were found to differ between groups. For instances that met these requirements, group status would be entered at step 1, and the relevant perseverative cognition variable at step 2. For each regression, it was predicted that the perseverative cognition variable added at step 2

would be significantly associated with individual differences in recovery, and that group status would no longer explain significant independent variance in recovery at step 2. Finally, in order to test for a potential interaction effect between group status and perseverative cognition, an interaction term would be entered at step 3. It was anticipated that there would be no significant change in variance explained at this step. All regression models were checked for linear relationships between variables, homoscedasticity, and absence of outliers/leverage in residuals.

2.7.4 Sensitivity Analyses

2.7.4.1 Sensitivity analyses for potential covariates. For any significant results on the primary outcome measures of recovery and habituation, the next step involved running additional hierarchical regression analyses to determine whether the relationship between group status and the dependent variables would be explained by the covariates mentioned previously: depression and anxiety symptomatology, BMI, current life stress, and age. Two-step hierarchical regression analyses would be created entering the group variable at step 1, the potential covariate at step 2, and an interaction between the two at step 3. If the addition of the covariate or interaction term at either step 2 or 3 resulted in a significant decrease in variance explained by group, we would report these results further investigate the relationship between the covariate and the relevant dependent variable using simple regression.

2.7.4.2 Sensitivity analyses using migraine frequency as a predictor. Due to the relatively low frequency of migraines experiences by some participants in the MI group (e.g., one third of participants reporting <1 headache day/month), we conducted ancillary analyses investigating relationships between migraine and primary autonomic outcome measures in the full sample using a continuous measure of migraine frequency in place of Group. (Frequency was set to zero

for all controls.) Within the MI sample, we also examined associations between physiological outcomes and two other headache severity variables: age of migraine onset and migraine symptom load. The symptom load variable was created to quantify both number of symptoms experienced and functional impact of migraines[7]. These analyses primarily consisted of Spearman's rho correlations, as the migraine frequency variable had a non-normal distribution that made it inappropriate for parametric tests. Associations between migraine frequency and habituation were conducted using habituation slope values so that each participant could be assigned a single value.

2.7.4.3 Sensitivity analyses using continuous time series as a dependent variable. Because the methods of data reduction described thus far involve collapsing data across various periods of time, it is possible that this could result in a loss of information about the time-course of physiological changes. In order to identify and examine any potentially meaningful group differences between MI and HC groups in overall arousal level during all epochs of interest, additional comparisons of sympathetic and parasympathetic activity were conducted across all time-points of the stressor and recovery periods, as has been done in previous work from this lab (Mandell, Siegle, Shutt, Feldmiller, & Thase, 2014).

The data entered into these analyses consisted of second-by-second incongruent and recovery time series for SCL and HF-HRV. The HRV time series were created using MindWare's Real Time data analysis function; second-by-second values for this measure consisted of moving averages using a 30-second buffer. To accommodate missing data for this window at the end of some participants' recovery time series, only the first 4 minutes (240

[7] Migraine symptom load was a composite of migraine symptom counts (e.g., pulsating or throbbing pain, nausea, photophobia, etc.), one dichotomous item assessing functional impairment from migraines in the past month, and one continuous variable assessing typical migraine duration.

seconds) of data are presented here. PEP were derived from ensemble averages (10 second averages in the present study), and therefore second-by-second time series could not be calculated for this variable. Using the ensemble averages as time series values would have resulted in a much smaller number of values per time period (e.g., only 8 values for each incongruent trial) than would be necessary to calculate autocorrelation values needed for the thresholding procedure described below.

To control for Type I error across so many observations, the results of these analyses were subjected to temporal contiguity thresholding procedures, such that statistical group differences were considered "significant" only if they persisted for a sufficient duration[8]. Briefly, we followed Guthrie and Buchwald's (Guthrie & Buchwald, 1991) procedure to determine how many consecutive time points would need to be significant at the $p < .05$ to produce an interval of a length that was significant at $p < .05$. This method of temporal contiguity thresholding allows us to control type I error inflation by accounting for high levels of autocorrelation found in continuous psychophysiological measures.

[8] For each of the two time series measures (SCL, HRV) for both the recovery period and incongruent periods, separate temporal "windows" of significant differences were identified by generating a t-test statistic for the difference between groups means at each one-second time-point for the duration of the period (e.g., 80 t-tests for each 80-second incongruent trial). To control for Type I error, test statistics were subjected to temporal contiguity thresholds that required a certain number of consecutive time points significant at $p<.05$ in order for any of the component time points to be considered significant. This threshold was derived via randomization tests (1000 simulations in which observed waveforms were randomly assigned to subjects) for the number of consecutive time points that would occur by chance at this level at $p<.05$. Thus, for SCL analyses, sufficient group difference windows were defined as any sequence of consecutive group differences (individually significant at $p<.05$) that lasted at least 11 consecutive time points (for incongruent), or at least 53 time-points (for recovery).For HRV analyses, sufficient group difference windows were defined as any sequence of consecutive group differences (individually significant at $p<.05$) that lasted at least 16 consecutive time points (for incongruent), or at least 27 consecutive time-points (for recovery).

3.0 RESULTS

3.1 PARTICIPANT CHARACTERISTICS

Characteristics of the sample can be found in Table 2. Statistics for all indices are only reported for individuals who has useable psychophysiological data on at least one of the three primary dependent measures. The average age of the sample was 18.6 years old, with 76.4% of participants identifying as Caucasian. In an unfortunate data collection error, the SES measure was not included in the original questionnaire battery, and therefore SES data were only collected for the last 49 participants (25 HC, 24 MI). The average participant in this sub-sample described her family as being between middle- and upper-middle class income, with parents who obtained some type of college degree. Average BMI was in the high healthy range (M = 24.03 ± 3.63 [SD]), with 15 participants falling into the overweight range (BMI of 25-29.9), and five falling into the obese range BMI > 30. As BMI has been shown to affect cardiovascular variables, all primary aims analyses of PEP and HRV were repeated after excluding these participants. Overall, participants reported a relatively high level of recent life stress (M = 19.43 ± 6.10). On average participants reported getting approximately seven hours of sleep the previous night. Less than half the sample (42.3%) reported consuming any caffeine at all (however 6 participants received a caffeine loading score of over 200mg[9]).

[9] All primary analyses on autonomic outcomes were re-run to ensure that excluding these subjects did not result in a substantial change in results. As findings did not change substantively after removing these subjects (magnitude of *change* in *p* values was .005-.13), these results are not reported here.

Table 2

Demographic and Health-Related Variables across the Full Sample

Measure	Sample Mean	Range	Count	Percent (%)
Age	18.61	18 - 22		
Race				
Caucasian			55	76.4
African-American			7	9.7
Asian/Pacific Islander			6	8.3
Hispanic			2	2.8
Mixed race			2	2.8
Socioeconomic status (SES)*	.609	.07 - .89		
Body mass index (BMI)	24.03	15.3 - 35.5		
Current life stress (PSS)	19.43	6 – 34		
Previous night sleep (# of hours)	6.91	3 – 10		
Estimated caffeine load (mg)	66.8	0 – 370		

Note: BMI = body mass index; **N* = 49 for analyses of SES; for all other variables, *N* = 72

Group means for demographic and health-related variables can be found in Tables 3 and 4, respectively. Table 4 includes means for psychological symptom measures. Participants in the MI group were non-significantly older than those in the HC group ($p = .09$), and no group differences emerged between MI and HC groups on the composite student SES statistic, and differences in racial demographics for each cell (e.g., Caucasian, African American, etc.) were not statistically significant (as calculated by Fisher's exact tests; p's >.2).

Table 3

Group Descriptive Statistics for Demographic Variables

Measure	**HC**	**MI**	**HC Count (%)**	**MI Count (%)**	**Group differences**
N	37	35			
Age	(Mdn) 18	(Mdn) 19			$U = 781$, $z = .05$ $p = .09$
Race					
Caucasian			28 (75.7)	27 (77.1)	$p = 1.0$
African-American			2 (5.4)	5 (14.3)	$p = .254$
Asian/Pacific Islander			5 (13.5)	1 (2.9)	$p = .201$
Hispanic			1 (2.7)	1 (2.9)	$p = 1.0$
Mixed race			1 (2.7)	1 (2.9)	$p = 1.0$
SES*	(Mdn) .643	(Mdn) .669			$U = 602.5$, $z = .05$, $p = .96$

Note: *$N = 49$ for analyses of SES; HC=health controls; MI=migraineurs.

Table 4

Group Descriptive Statistics for Health-Related Variables

Measure	**HC Mean**	**MI Mean**	**Group differences**
N	37	35	
BMI	24.14 ± 3.65	23.93 ± 3.66	$t(70) = .26$, $p = .80$, $d = .06$
Sleep (# of hours)	(Mdn) 7	(Mdn) 7	$U = 524.5$, $z = -1.43$, $p = .15$
Caffeine load (mg)	(Mdn) 0	(Mdn) 0	$U = 600$, $z = -.37$, $p = .71$
PSS	**17.97 ± 5.38**	**20.97 ± 6.50**	***t*(70) = -2.14, *p* = .04, *d* = -.51**
PROMIS Anxiety	56.98 ± 6.49	59.75 ± 8.58	$t(70) = -1.55$, $p = .13$, $d = -.37$
PROMIS Depression	48.15 ± 8.23	50.14 ± 9.34	$t(70) = -.96$, $p = .34$, $d = -.23$
7 Up (Mania)	4.78 ± 2.96	4.94 ± 3.60	$t(70) = -2.05$, $p = .84$, $d = -.04$

Note: Means ± SD; HC=health controls; MI=migraineurs; PSS = Perceived Stress Scale; PROMIS-A = PROMIS Anxiety Scale; PROMIS-D = PROMIS Depression Scale; 7 Up (Mania) = 7 Up 7 Down Inventory - Mania symptom subscale.

MI participants reported significantly higher levels of recent life stress (p = .04) than did HC participants. Despite non-significant t statistics, anxiety and depression symptom measures showed small to medium effect sizes (anxiety: Cohen's d = -.37; depression: Cohen's d = -.23), with MIs reporting slightly higher levels of both. There are no specific clinical cutoff scores for the PROMIS measures used here, however based on population norms for young adults, both groups' means very close to the population mean on depression scores; for anxiety scores, MI and HC groups fell approximately 1 SD and .7 SD above the population mean, respectively (e.g., 82nd and 77th percentile)[10]. There were also no significant group differences in BMI, self-reported sleep, caffeine consumption, or symptoms of mania.

3.1.1 Headache Characteristics in Migraineurs

Within the MI group, participants reported experiencing an average of 1.94 migraine episodes per month (SD=1.77). Eleven individuals (31.4%) reported that they had been diagnosed with migraines by a medical professional (7 by a primary care physician; 5 by a neurologist), while another 7 participants (20%) were unsure of whether they had received a formal diagnosis. Average self-reported age of onset for migraines was 14.17 (SD = 2.44). MIs who reported an earlier age of onset also reported higher levels of depression symptoms, $r(35) = -.41$, p =.01. Thirty-two participants (91.4%) reported stress as a major trigger for their migraines. Other commonly endorsed triggers included sleep disruptions (68.6%), not eating (48.6%), weather (28.6%), hormonal changes (25.7%), and neck tension (25.7%).

[10] The PROMIS scores represent T scaled scores, meaning that the mean score in the general population = 50 with SDs of 10.

3.2 STRESSOR TASK BEHAVIORAL DATA

Mean reaction times and percent (%) accuracy statistics for the Incongruent periods of the Stroop task are presented in Table 5. Data from the congruent periods were not explored here as they were not the epoch of interest and primarily served as an active "break" period in between stressor blocks. The sample as a whole performed more quickly with each successive block, as demonstrated in a main period effect: $F(1.64, 98.12) = 17.33$, $p < .001$, $\eta_p^2 = .47$. There was no significant period effect on the accuracy rate, confirming that the computer program running the task had successfully adapted the task demands to maintain participants' performance at an overall accuracy rate of ~60%.

3.2.1 Emotion Valence and Stress Appraisal Ratings

To assess participants' subjective experiences of the stressor task, VAS ratings taken at Baseline, Post-training (Pre-task), and Post-recovery were subjected to repeated-measures ANOVAs. A full account of group means and inferential statistics for the four subjective ratings of interest (e.g., Stressed, Frustrated, Anxious, and Tired) can be found in Appendix A, Table 1. After family-wise error correction (Bonferroni-corrected $\alpha = .0125$), significant effects of Time[11] indicated that both groups experienced task-related increases in anxiety, $F(2,130) = 16.18$, $p < .001$, and frustration, $F(2,128) = 26.51$, $p < .001$. There was also significant Group x Time interaction on Stressed ratings, $F(2,130) = 4.70$, $p = .01$, with MI participants feeling significantly more stressed than controls in the period immediately preceding the stressor task $F(2,130) = 4.70$, $p = .01$[12].

[11] The term "Time" is intentionally applied to differentiate time points at which participants made their VAS ratings (Baseline, Pre-Stressor, and Post-Recovery), from the "Period", which refers to task periods themselves (Incon1, Incon2, Incon3).

[12] Bonferroni-corrected α level = .05/3 = .0167 (for three mean comparisons across time points).

Table 5

Reaction Times and Accuracy Rates across Stressor Task Blocks

		Group Means		Period effect			Group effect			Group x Period effect		
	Period	**HC**	**MI**	**F**	***p***	**η_p^2**	**F**	***p***	**η_p^2**	**F**	***p***	**η_p^2**
RTs	Incon1	1051.2 ± 325.1	1100.5 ± 373.1	**17.33***	**<.001***	**.47**	1.49	.23	.02	.01	.98	.00
	Incon2	916.8 ± 210.0	962.4 ± 237.5									
	Incon3	846.3 ± 162.1	899.4 ± 195.9									
% Acc	Incon1	61.9 ± 11.1	57.2 ± 14.7	1.28	.28	.02	1.88	.18	.03	.46	.61	.01
	Incon2	62.3 ± 11.5	58.9 ± 11.2									
	Incon3	63.0 ± 10.0	61.4 ± 12.7									

Note: Harmonic means ± SD; *= Significant at Bonferroni-corrected α level of .025; RTs = reaction times; % Acc = percentage of items accurate

Participants also completed appraisals of the stressor task itself after completing training but just prior to beginning the task. Means and inferential statistics for participants' self-reported appraisals of the stressor task can be found in Table 6. MI participants rated the task as significantly more threatening than did HC participants (p = .02).

Table 6

State and Trait Stress Appraisal Ratings by Group

Measure	**HC Mean**	**MI Mean**	**t**	**p**	**Cohen's d**
SAM - Threat[a]	1.76 ± .51	2.10 ± .69	-2.39*	.02*	-.57
SAM – Challenge[a]	1.76 ± .65	1.95 ± .68	-1.23	.22	-.29
SAM - Control by self[a]	3.46 ± .72	3.30 ± .89	.84	.40	.10
CAS – Threat[b]	35.6 ± 10.8	32.4 ± 11.4	1.23	.22	.29
CAS – Challenge[b]	36.2 ± 5.4	37.4 ± 4.4	-.99	.33	-.24

Note: Means ± SD; HC=health controls; MI=migraineurs; *****= Significant at Bonferroni-corrected α level of .017.; [a] = Family-wise error correction = .05/3 = .017; [b] = Family-wise error correction = .05/2 = .025; SAM = Stress appraisal measure; CAS = Cognitive appraisal scale.

3.3 PRELIMINARY PHYSIOLOGICAL ANALYSES

Table 7 contains group means for baseline sympathetic and parasympathetic activation. For descriptive purposes, bivariate correlations were calculated to examine associations between sample demographic and health-related characteristic and baseline autonomic variables. These correlations can be seen in Appendix E, Table 1. We did not apply additional family-wise error rate correction to these exploratory correlations, as were primarily intended to assess generalizability in our sample by replicating previously reported demographic associations (e.g., depression's association with decreased HRV).

Table 7 also contains results of independent samples *t*-tests performed on baseline values, which revealed no significant group differences in baseline SC (p = .92, d = .03), PEP, (p = .57, d = -.14), or HF-HRV (p = .19, d = .32). Removing participants with a BMI > 30 from analyses of cardiovascular variables did not result in significant changes to these results (Appendix B).

Table 7

Baseline Sympathetic and Parasympathetic Values by Group

Measure	HC Mean	MI Mean	df	*t*	*p*	Cohen's *d*
SCL	10.19 ± 5.77	10.04 ± 5.81	63	.10	.92	.03
PEP	114.39 ± 8.20	115.52 ± 7.86	65	-.58	.57	-.14
ln HF-HRV	6.51 ± .72	6.23 ± .83	66	1.32	.19	.32

Note: Means ± SD; HC=health controls; MI=migraineurs; SCL=skin conductance level; PEP=pre-ejection period; ln HF-HRV= high-frequency heart rate variability (natural log).

Table 8 contains group means and results for preliminary repeated measures ANOVAs. Figures 3, 4, and 5 display plots of mean autonomic activity by group across baseline and incongruent periods. On sympathetic measures, there were no significant Group x Period interaction effects for either SCL (p = .75), or PEP (p = .47) indicating that MI and HC groups

did not differ from one another in patterns of sympathetic reactivity to the stressor task. In addition, there were no main effects of group for either SCL (p = .84), or PEP, p = .92. Main effects of Period showed significant increases in SCL, F(1.56, 98.02) = 78.01, p < .001, ηp2 = .55, (see Figure 3), and decreases in PEP, F(1.56, 101.15) = 48.81, p < .001, ηp2 = .43 (see Figure 4), consistent with increased sympathetic activity.

For each measure, Bonferroni-corrected pairwise comparisons were conducted on period values collapsed across group to determine which blocks differed significant from one another. As illustrated in Figure 3, SCL increased significantly from baseline to Incon1 for both groups (p < .001), then decreased significantly from Incon1 to Incon2 (p < .001). Incon3 did not differ from Incon2 (p =1.0). For all incongruent periods, SCL was significantly elevated above baseline (all p's < .001). As illustrated in Figure 4, PEP showed a significant decrease from baseline to Incon1 (p < .001), followed by significant successive increases at Incon2 (p < .001) and Incon3 (p < .001). For all incongruent periods, PEP remained significantly lower than baseline (all p's <.001).

Table 8

Autonomic Responses Across Baseline and Incongruent Stressor Task Periods by Group

		Group Means		Period effect			Group effect			Group x Period effect		
Measure	**Period**	**HC**	**MI**	**F**	***p***	**η_p^2**	**F**	***p***	**η_p^2**	**F**	***p***	**η_p^2**
SCL	Baseline	10.19 ± 5.77	10.05 ± 5.81	78.01*	<.001*	.55	.04	.84	.00	.22	.75	.00
	Incon1	13.97 ± 6.04	13.87 ± 4.98									
	Incon2	13.05 ± 5.5	12.65 ± 5.11									
	Incon3	12.97 ± 5.56	12.55 ± 5.16									
PEP	Baseline	114.39 ± 8.2	115.52 ± 7.86	48.81*	<.001*	.43	.01	.92	.00	.69	.47	.01
	Incon1	107.97 ± 9.82	108.16 ± 8.30									
	Incon2	110.75 ± 9.11	110.25 ± 7.79									
	Incon3	111.77 ± 8.76	111.75 ± 8.20									
HRV	Baseline	6.51 ± .71	6.27 ± .83	20.76*	<.001*	.24	5.64*	.02*	.08	2.44	.07	.04
	Incon1	6.15 ± .92	5.44 ± 1.03									
	Incon2	6.07 ± .85	5.66 ± .95									
	Incon3	6.06 ± .94	5.58 ± 1.06									

Note: Means ± SD; * = $p < .05$, ** = $p < .01$; HC=health controls; MI=migraineurs; SCL=skin conductance level; PEP=pre-ejection period; HRV= heart rate variability.

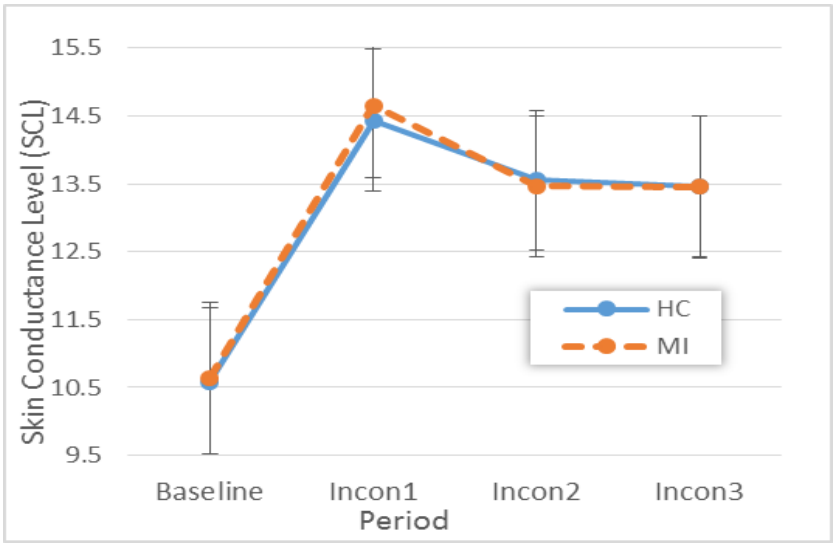

Figure 3. Mean skin conductance level values in migraineurs (MI) and healthy controls (HC) across baseline and incongruent periods.

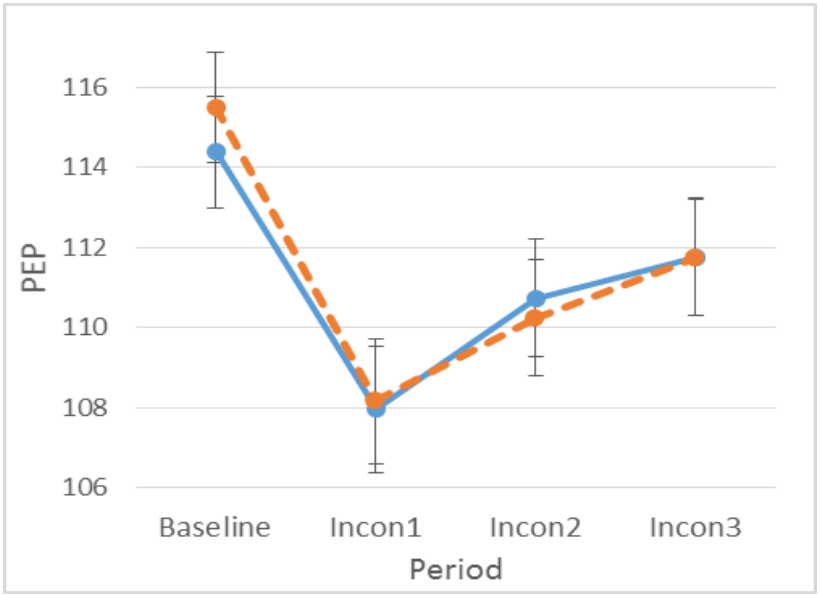

Figure 4. Mean pre-ejection period values in migraineurs and healthy controls across baseline and incongruent periods.

As shown in Figure 5, with respect to parasympathetic responses a main effect of Period indicated significant task-related changes in ln HF-HRV, $F(2.65, 174.97) = 6.15$, $p < .001$, $\eta_p^2 = .24$. Bonferroni-corrected pairwise comparisons indicated that all three incongruent periods were significantly lower than baseline (p's < .001), suggesting that the task resulted in significant vagal withdrawal across all incongruent blocks. Incongruent blocks, however, did not differ significantly from one another (p's = 1.0). Unlike for sympathetic outcome measures, ln HF-HRV analyses revealed a significant effect of group, $F(1, 66) = 5.64$, $p = .02$, $\eta_p^2 = .08$, and a non-significantly greater vagal withdrawal demonstrated by the MI group across all periods, Group x Period interaction effect, $F(2.65, 174.97) = .22$, $p = .07$, $\eta_p^2 = .04$.

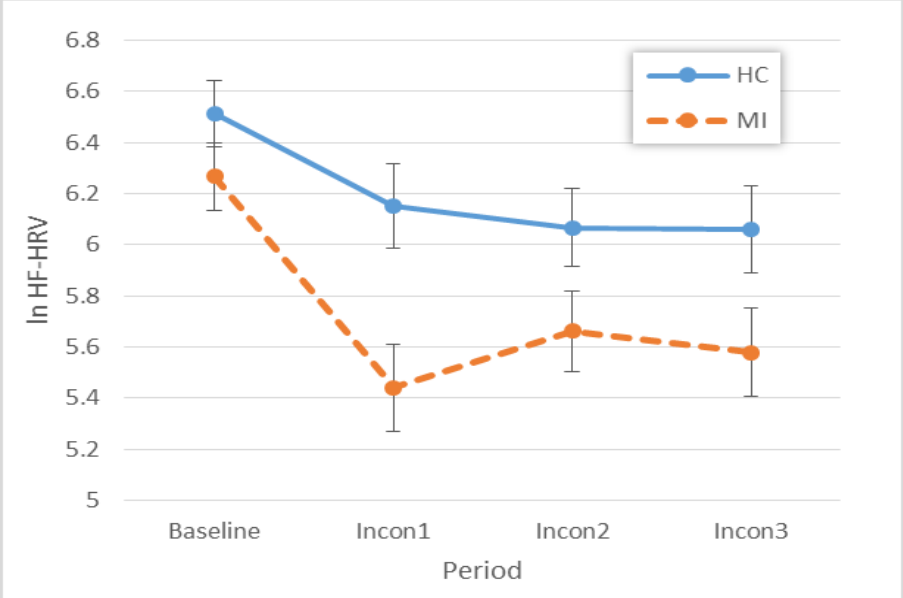

Figure 5. Mean parasympathetic activity (natural log of high frequency heart-rate variability [ln HF-HRV]) in migraineurs (MI) and healthy controls (HC) across baseline and incongruent periods.

Removing participants with a BMI > 30 led to no substantive changes in preliminary results for PEP and HRV (see Appendix B for relevant tables of adjusted means and statistics), other than a decrease statistical power making the marginal Group x Period interaction for HRV non-significant (p = .11).

3.4 PRIMARY AIM 1: GROUP DIFFERENCES IN AUTONOMIC RECOVERY

3.4.1 Hypothesis 1a: Decreased Sympathetic Recovery

Primary hypothesis 1a posited that migraineurs would show decreased sympathetic recovery during the post-stress recovery period, as indexed by smaller reductions in sympathetic arousal relative to controls**.** Group differences in recovery across the 5-minute recovery period were investigated by comparing mean values for the three gamma function parameters (α, β, and height). Larger α parameter values suggest a longer delay to recovery; larger β values suggest a flatter, shallower time course; larger or smaller values on the height parameter suggest the magnitude of recovery that occurs on average over the period[13]. In the present sample, the α parameter for SCL and the β parameters for SCL and PEP were not normally distributed and therefore Mann-Whitney U tests were run in place of independent sample *t*-tests for these analyses. Results of group comparisons for all of these parameters can be found in Table 9.

[13] For the present study variables, blunted or incomplete recovery would be indicated by smaller values on the height parameter for PEP and larger values on this parameter for SCL.

Table 9

Sympathetic Recovery – Group Comparisons of Gamma Function Parameters

DV	Parameter	HC Mean (Mdn)	MI Mean (Mdn)	Group differences
SCL	α (offset)	(-.008)	(-.014)	U =453, z =-.59, *p* =.55
	β (rise-decay)	(468.97)	(5234.57)	U =453, z =-.59, *p* =.55
	Height			*t*(56) = -.40, *p* = .70, *d* = -.11
PEP	α (offset)	.024 ± .022	.025 ± .018	*t*(61) = -.39, *p* = .70, *d* = -.10
	β (rise-decay)	(3477.74)	(1008.81)	U = 352, *z*= -1.44, *p* = .15.
	Height	116.33 ± 6.44	116.20 ± 8.40	*t*(61) = .8, *p* = .39, *d* = .22

Note: HC=health controls; MI=migraineurs; SCL=skin conductance level; PEP=pre-ejection period. Analyses included data only on participants whose gamma fit was reliable (SCL: *N* = 58; PEP: *N* = 63)

For SCL recovery analyses, Mann-Whitney U-tests showed no significant differences between HC and MI groups for the α-parameter (*p* =.55), or β-parameter, (*p* = .61)[14]. Independent sample *t*-tests showed no group differences in the height parameter, (*p* = .84). These results suggest that there were no mean group differences in the time to onset of recovery, shape of the recovery curve (e.g., flat vs. rounded), or the level of recovery attained.

For PEP recovery analyses, a Mann-Whitney U statistic for the β parameter was non-significant, (*p* = .15)[15]. Independent sample *t*-tests showed no group differences in the α-parameter, (*p* = .70), or the height parameter, (*p* = .39). Thus, results of these analyses showed no evidence that MI and HC group had different shaped recovery curves, as indexed by gamma function parameters. Removing participants with a BMI > 30 led to no substantive changes in results for PEP recovery (see Appendix B, Table 3).

[14] Effect sizes for Mann-Whitney U-tests (calculated as $r = z/\sqrt{N}$): SCL α: *r* = - .07; SCL β: *r* = .07.
[15] Effect sizes for Mann-Whitney U-tests (calculated as $r = z/\sqrt{N}$): PEP β: *r* = -.19

3.4.2 Hypothesis 1b: Decreased Parasympathetic Recovery

To determine if migraineurs show decreased parasympathetic recovery during the post-stress recovery period—as indexed by diminished parasympathetic rebound relative to controls—**g**roup means were compared for both final vagal rebound (i.e., rebound from Incon3 to Recovery minute 1) and peak vagal rebound (i.e., rebound from the lowest value of Incon1, Incon, or Incon3 to Recovery minute 1). There were no significant group differences in vagal rebound values for either final vagal rebound, $t(66) = -.82$, $p = .41$, $d = -.20$, or for peak vagal rebound (e.g., vagal rebound from peak vagal withdrawal), $t(66) = -.69$, $p = .49$, $d = -.17$.

3.5 PRIMARY AIM 2: GROUP DIFFERENCES IN SYMPATHETIC HABITUATION

3.5.1 Hypothesis 2: Decreased Habituation to a Repeated Stressor

Primary hypothesis 2 posited that migraineurs would show decreased habituation to a repeated stressor, as indexed by smaller decreases in sympathetic arousal across multiple presentations of a repeated stressor relative to controls. To test for differential habituation in MI and HC groups, 2 x 3 repeated measures ANCOVA analyses were run with the three Incongruent task periods as the repeated measure. To control for individual baseline and initial levels of stressor-induced reactivity, these variables were entered as covariates. Group x time interaction would be indicative of differential habituation between migraineurs and controls.

Figures 6 and 7 contain estimated marginal means for sympathetic measures at each of the three incongruent trials after controlling for individual differences in baseline and initial reactivity (e.g., change from baseline to Incon1). As shown in Table 10, after controlling for individual differences in Baseline and Initial reactivity values, there were no significant Group x

Period interaction effects for analyses of SCL, (p = .42), or PEP (p = .42). Removing participants with a BMI > 30 led to no substantive changes in results for PEP habituation (see Appendix B, Table 5). Based on visual inspection, between trial habituation appeared to occur primarily between Incon1 and Incon2 for SCL. PEP response appeared to continue habituating from Incon2 to Incon 3 as well.

Table 10

Habituation Model: Group x Period Interaction Effects

Measure	**Group x Period effect**					
	N	***df* 1**	***df* 2**	***F***	***p***	η_p^2
SCL	65	1.71	104.34	.833	.42	.01
PEP	67	1.77	109.99	.835	.42	.01

Note: SCL=skin conductance level; PEP=pre-ejection period.

Note: HC=health controls; MI=migraineurs; SCL=skin conductance level; PEP=pre-ejection period.

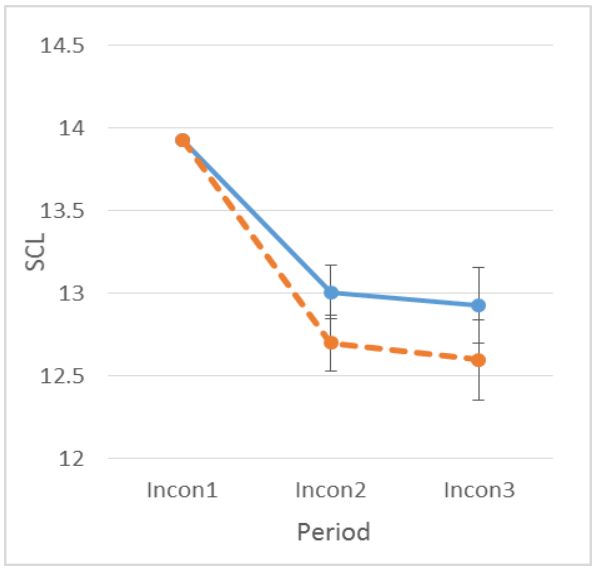

Figure 6. Estimated marginal means for repeated measures of skin conductance level (SCL) controlling for baseline and initial reactivity. Error bars indicate standard errors for estimated marginal means. (Controlling for baseline and initial reactivity functioned to set all subjects' Incon1 to the same value, thus the standard error for Incon1 is zero for both groups.)

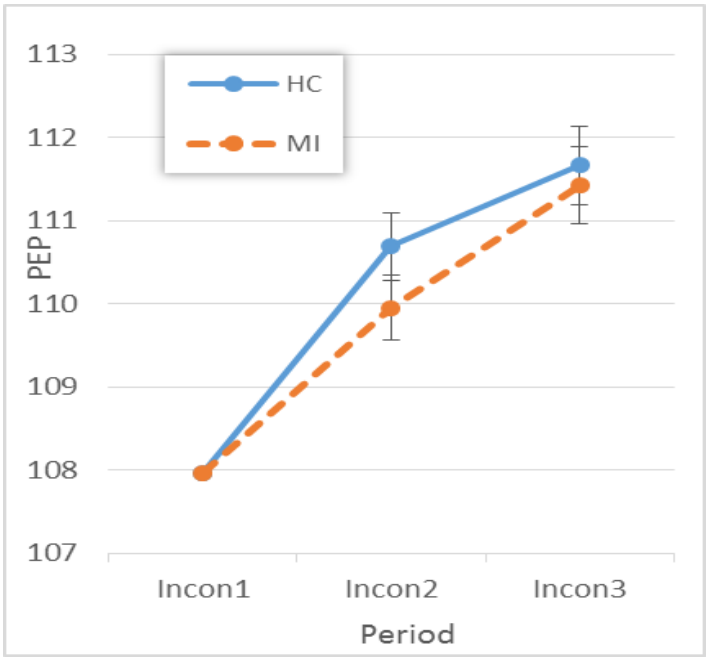

Figure 7. Estimated marginal means for repeated measures of pre-ejection period (PEP) controlling for baseline and initial reactivity. Error bars indicate standard errors for estimated marginal means. (Controlling for baseline and initial reactivity functioned to set all subjects' Incon1 to the same value, thus the standard error for Incon1 is zero for both groups.)

3.5.1.1 Parasympathetic habituation. Habituation ANCOVA analysis was also performed on ln HF-HRV, however in this case, group differences were found in task-related reactivity (e.g., vagal withdrawal). Under these circumstances, interpreting the Group x Period interaction term alone (as we did with sympathetic habituation analyses) could result in an under-estimation of the effects of group upon changes in HRV after initial reactivity. Examination of the covariates and their interaction terms in the present model confirmed the predictable finding that individual differences in HRV at baseline and more so in initial vagal reactivity to stress could explain the vast majority of variance in someone's *current* HRV. All examine interaction effects were only significant to the extent that they involved initial HRV reactivity (e.g., Group x Period x Reactivity: $F(4, 128) = 8.10$, $p < .001$). The Group x Period x Baseline interaction, in contrast, was non-significant $F(4,128) = .86$, $p = .49$. We therefore turn our attention to cognitive factors that may influence patterns of recovery and potentially changes in reactivity over time.

3.6 SECONDARY AIM 1: GROUP DIFFERENCES IN PERSEVERATIVE COGNITION

3.6.1 Hypothesis SA1a: Higher Levels of Trait Perseverative Cognition

Secondary hypothesis 1a posited that migraineurs would report higher-levels of trait perseverative cognition (worry and rumination) than controls. Table 11 contains group results for perseverative cognition variables, including trait worry and rumination, and state measures of task-related (TRT) and task-unrelated perseverative cognition (TUT). Results indicate that MIs did not differ significantly from HCs in terms of the amount of trait worry (p = .22, Cohen's d = -.29), or trait rumination they experience (p = .44, Cohen's d = -.18)

Table 11

Group Means for State and Trait Perseverative Cognition Variables

	HC		**MI**		**Group differences**		
Measure	**Mean**	**SD**	**Mean**	**SD**	**t**	***p***	***d***
RRQ (Trait Rumination)	40.11	8.61	41.71	9.03	-.77	.44	-.18
PSWQ (Trait Worry)	48.95	11.69	52.54	13.02	-1.24	.22	-.29
Baseline TUT [a]	18.16	3.99	17.12	4.56	1.23	.22	.29
Post-stressor TUT [a]	**17.11**	**4.19**	**14.89**	**3.11**	**2.54***	**.01***	.61
Post-stressor TRT [a]	16.59	4.69	17.12	4.56	-.48	.63	.06

Note: HC=health controls; MI=migraineurs. N=70; *****= Significant at Bonferroni-corrected α level of .017.; [a] = Family-wise error correction = .05/3 = .017

3.6.2 Hypothesis SA1b: Higher Levels of State Perseverative Cognition

Secondary hypothesis 1b posited that migraineurs would report higher levels of state (e.g., stressor-specific) perseverative cognition than controls during the recovery period. Results indicate that MIs did not differ significantly from HCs in terms of perseverative task-unrelated thought at baseline (p = .22, Cohen's d = .29), or perseverative task-related thought after the stressor task, (p = .63, Cohen's d = .06). Unexpectedly, following the stressor task, HCs reported significantly more task-unrelated perseveration (TUT) than MIs (p = .01, Cohen's d = .61). Figure 8 illustrates the change in TUT between Baseline and Recovery periods for both groups.[16]

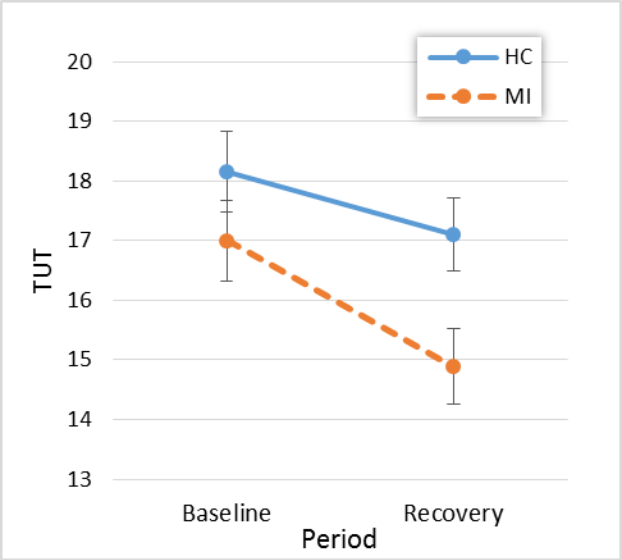

Figure 8. Group scores on measures of Task-Unrelated Thought (TUT) during baseline and post-stress recovery periods.

[16] Unplanned follow-up analyses entering TUT data into a 2 (Group: HC, MI) x 2 (Period: Baseline x Post-stressor) revealed significant main effects of Group, F (1,70) = 4.41, p = .04, and Period, F (1,70) = 14.04, p < .001, but no significant Group x Period interaction, F = 1.57, p =.21.

3.7 SECONDARY AIM 2: RELATING SELF-REPORT AND PHYSIOLOGICAL MECHANISMS OF AUTONOMIC RECOVERY AND HABITUATION

3.7.1 Hypothesis SA2a: Trait Stress Appraisal as a Moderator

To examine whether trait stress appraisal moderates the relationship between migraine status and habituation, hierarchical linear regression analyses were used to investigate whether the relationship between group and habituation slope differs as a function of appraisal (see Tables 12-15). Based on evidence from preliminary analyses that SCL decreased rapidly for all participants from Incon1 to Incon2, but not from Incon2 to Incon3, we concluded that SCL habituation occurred only between Incon1 and Incon2 for most subjects. Thus, the slope used for SCL habituation analyses consisted of the Incon1-Incon2 slope. The slope used for PEP habituation analyses was also the slope between Incon1 and Incon2, as the larger habituation (i.e., overall increase in PEP values) appeared to occur at this phase. Because there was still considerable habituation between Incon2 and Incon3, however, statistics for regression models for the full slope between Incon1 and Incon3 slope can be found in Appendix C. These results were broadly non-significant.

Table 12

Linear Regression of Skin Conductance Level Slope (Incon1-Incon2) on Group x Trait Threat Appraisal Interaction

	B	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**ΔF**	**Sig. ΔF**
Step 1					0.04	0.04	1.33	0.27
Group	-0.26	0.26	-0.13	0.31				
Trait Threat Appraisal	-0.1	0.22	-0.06	0.65				
Step 2					0.05	0.01	0.59	0.45
Group	-0.23	0.27	-0.11	0.39				
Trait Threat Appraisal	0.01	0.01	0.15	0.26				
Group x Trait Appraisal	-0.14	0.27	-0.07	0.61				

Note: N = 65; Group coded: 0 = Control, 1 = Migraine

Table 13

Linear Regression of Pre-Ejection Period Slope (Incon1-Incon2) on Group x Trait Threat Appraisal Interaction

	B	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**ΔF**	**Sig. ΔF**
Step 1					.01	.01	.43	.65
Group	.68	.75	.11	.37				
Trait Threat Appraisal	.003	.04	.01	.92				
Step 2					.02	.00	.14	.71
Group	.67	.76	.11	.38				
Trait Threat Appraisal	-.03	.11	-.12	.75				
Group x Trait Appraisal	.03	.07	.14	.71				

Note: *N* = 67; Group coded: 0 = Control, 1 = Migraine

Table 14

Linear Regression of Skin Conductance Level Slope (Incon1-Incon2) on Group x Trait Challenge Appraisal Interaction

	B	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**ΔF**	**Sig. ΔF**
Step 1					.08	.08	2.57	.09
Group	-.28	.75	-.12	.33				
Trait Challenge Appraisal	-.05	.08	.06	.62				
Step 2					.10	.03	1.69	.20
Group	-.27	.25	-.13	.28				
Trait Challenge Appraisal	-.02	.03	-.11	.49				
Group x Trait Appraisal	-.07	.05	-.20	.20				

Note: *N* = 65; Group coded: 0 = Control, 1 = Migraine

Table 15

Linear Regression of Pre-Ejection Period Slope (Incon1-Incon2) on Group x Trait Challenge Appraisal Interaction

	B	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**ΔF**	**Sig. ΔF**
Step 1					.02	.02	.55	.58
Group	-.73	.75	-.12	.33				
Trait Challenge Appraisal	.04	.08	.06	.62				
Step 2					.02	.00	.03	.86
Group	-.72	.75	-.12	.34				
Trait Challenge Appraisal	.05	.10	.08	.62				
Group x Trait Appraisal	-.03	.16	-.03	.86				

Note: *N* = 67; Group coded: 0 = Control, 1 = Migraine

Results from hierarchical regression analyses entering Group x Trait Threat Appraisal interaction terms at step 2 (see Tables 12-13) indicated that trait threat appraisal did not moderate the relationship between migraine status and SCL habituation slope ($\Delta R^2 = .01$), nor the relationship between migraine status and PEP habituation slope ($\Delta R^2 = .002$). For the SCL regression, examination of studentized deleted residuals derived from step 2 of the model revealed three participants with residuals between -2.5 and -2.0. Removing these individuals from the analysis had no impact on the interaction at step 2[17].

Results from hierarchical regression analyses entering Group x Trait Challenge Appraisal interaction terms at step 2 (see Tables 14-15) indicated that trait threat appraisal did not moderate the relationship between migraine status and SCL habituation slope ($\Delta R^2 = .01$), nor the relationship between migraine status and PEP Incon1-Incon2 habituation slope ($\Delta R^2 = .002$)[18]; in addition, trait challenge appraisal also did not significantly moderate the relationship between migraine status and SCL habituation slope ($\Delta R^2 = .03$), nor the relationship between migraine status and PEP habituation slope ($\Delta R^2 = .002$)[19].

3.7.2 Hypothesis SA2b: State Stress Appraisal as a Moderator

To examine whether state (e.g., stressor-specific) stress appraisals moderate the relationship between migraine status and autonomic habituation, hierarchical linear regression analyses were run adding a Group x State Threat Appraisal interaction term at step 2 after accounting for main

[17] Removing these outliers (resulting in $N = 62$) produced a Model 1 where marginally significant variance was explained (9.0%, $F[2,59] = 2.92$, $p = .06$) and the Group coefficient was significant at step 1 (b = -.50 ± .24, $p = .04$) and marginally significant at Step 2 (b = -.47 ± .24, $p = .06$). However, since these were not extreme outliers, and since the primary parameter of interest in these moderation analyses in the interaction term, these alternative results are not discussed in depth.

[18] Similar results for Trait Threat Appraisal and PEP Incon1-Incon3 habituation ($\Delta R^2 = .01$). – See Appendix C, Table 1.

[19] Similar results for Trait Challenge Appraisal and PEP Incon1-Incon3 habituation ($\Delta R^2 = .004$). See Appendix C, Table 2.

effects at step 1 (see Tables 16 and 17). Results from these analyses indicated that state threat appraisal did not moderate the relationship between migraine status and SCL habituation slope ($\Delta R^2 = .001$).

Table 16

Linear Regression of Skin Conductance Level Slope (Incon1-Incon2) on Group x State Threat Appraisal Interaction

	B	SE	β	*p*	R^2	ΔR^2	ΔF	Sig. ΔF
Step 1					.03	.03	.83	.44
Group	-.27	.27	-.13	.34				
State Threat Appraisal	-.10	.22	-.06	.65				
Step 2					.03	.00	.00	.96
Group	-.26	.28	-.13	.35				
State Threat Appraisal	-.12	.40	-.07	.77				
Group x State Appraisal	.03	.48	.01	.96				

Note: $N = 65$; Group coded: 0 = Control, 1 = Migraine

In the initial two-step model run for PEP habituation (see Table 17), the interaction term did not lead to a significant increase in variance explained ($\Delta R^2 = .02$)[20]. Upon inspection of regression diagnostics, two individuals were removed from the dataset for having very high studentized residual values (~4.0) and high leverage. When the regression analysis was re-run with these individuals removed, there was a non-significant increase in total variation explained with the addition of the interaction term ($\Delta R^2 = .05$). Model parameters and change statistics for both analyses (with and without outliers in the analysis) are shown in Table 17. The coefficient of the interaction term (-2.11 ± .1.15) was non-significant ($p = .07$) indicating that appraisal only weakly moderated the relationship between group membership and state threat appraisal[21].

[20] Similar results for State Threat Appraisal and PEP Incon1-Incon3 habituation ($\Delta R^2 = .02$). See Appendix C, Table 3.

[21] For the PEP Incon1-Incon3 habituation analysis, the coefficient of the interaction term was not significant (-1.84 ± .1.48, $p = .22$)

Simple slopes analysis revealed that the relationship between appraisal and habituation slope in migraine participants (b = -.22, SE = .61) was not statistically significant, (p = .717, but that there was a non-significant positive linear relationship (b = 1.89, SE = .66) between appraisal and habituation slope in HCs (p = .06). Conversely, this indicates that HCs who made more negative initial threat appraisals potentially experienced more rapid habituation between Incon1 and Incon2 than did MIs.

Table 17

Linear Regression of Pre-Ejection Period Slope (Incon1-Incon2) on Group x State Appraisal Interaction

Initial model (outliers included)	**B**	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**ΔF**	**Sig. ΔF**
Step 1					.01	.01	.42	.66
Group	-.67	.76	-.11	.38				
State Threat Appraisal	.25	.60	.05	.68				
Step 2					.03	.02	1.34	.25
Group	-.74	.77	-.12	.34				
State Threat Appraisal	1.18	1.00	.25	.24				
Group x State Appraisal	-1.44	1.24	-.24	.25				
Adjusted model (outliers removed)	**B**	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**ΔF**	**Sig. ΔF**
Step 1					.02	.02	.49	.61
Group	-.57	.67	-.11	.40				
State Threat Appraisal	.37	.53	.09	.48				
Step 2					.07	.05	3.35	.07†
Group	-.78	.66	-.15	.25				
State Threat Appraisal	1.89	.98	.47	.06†				
Group x State Appraisal	-2.1	1.15	-.43	.07†				

Note: N = 67 in Initial model; *N*=65 in Adjusted model; Group coded 0 = Control, 1 = Migraine; † = $p < .10$

3.7.3 Hypotheses SA2c and SA2d: Individual Differences in Trait and/or State Perseverative Cognition

Secondary hypotheses 2c and 2d posited that observed group differences in autonomic recovery would be explained by individual differences in trait and/or state perseverative cognition**.** As no significant group differences were found between MIs and HCs for either sympathetic or parasympathetic recovery, analyses for these hypotheses could not be conducted.

3.8 SENSITIVITY ANALYSES

None of the primary aims analyses produced significant results in the present sample, therefore no sensitivity analyses were run controlling for covariates in these outcomes (as it was assumed there would be even less variance explained by migraine status). However, in order to illustrate any zero order associations between our primary dependent variables and the proposed covariates, correlations between these variables were calculated.

Table 18 shows correlations between all proposed covariates and primary sympathetic and parasympathetic outcome variables. (Statistics displayed are Pearson *r* or Spearman rho correlations depending on the normality of the distribution for each variable.). There were significant correlations for two of the PEP recovery parameters: greater depression was associated with more delayed PEP recovery (as represented by the α-parameter), $r = -.34$, $p = .005$; and greater sleep time (in hours) was associated with a greater overall magnitude of recovery (as represented by the height parameter).

After running tests to ensure that covariates did not interact or covary significantly with Group and that final model residuals were normally distributed, step-wise linear regression

analyses were run with covariates entered first, followed by Group (using a dummy variable). Adding covariates to the model did not result in significant changes in outcomes; adding the Group parameter did not result in a significant increase in variance explained when entered after respective covariates[22] (after Depression in the recovery [α] model: $\beta = .12$, $\Delta R^2 = .01$, $p = .32$; after Sleep in the recovery [height] model: $\beta = -.03$, $\Delta R^2 = .01$, $p = .78$).

In addition, there was a significant negative correlation between participant age and both PEP (Incon1-Incon3) and SCL habituation, (PEP: $r = -.26$, $p = .04$; SCL: $r = -.26$, $p = .04$), which is unusual given that these two sympathetic measures have opposite directionality when it comes to arousal. This would seem to indicate that older participants are more likely to have decreased PEP habituation, but more complete SCL habitation. However, due to the non-normal distribution of the Age variable, hierarchical linear regression analyses could not be rerun entering it as a covariate (as the assumptions for such an analysis would not be met). Correlations between student SES and the β-parameters (rise-decay) for both SCL and PEP recovery would likely have been significant at the .05 level if mistakes in data collection had not resulted in missing data. This would have indicated that individuals with lower SES scores had significantly flatter recovery profiles.

3.8.1 Sensitivity Analyses Using Migraine Frequency as a Predictor

Given the relatively low frequency of headaches reported in our sample in contrast to other studies in the literature, sensitivity analyses were conducted to examine whether migraineurs with more frequent headaches are differentially more likely to demonstrate hypothesized patterns of prolonged autonomic stress response. We ran bivariate correlations between a continuous

[22] In these models, group membership was represented using a dummy variable in which MI = 1 and HC = 0.

measure of migraine frequency (# of migraines per month) and primary recovery and habituation variables in the full sample. (Individuals in the HC group were assigned a frequency value of zero). As with group comparisons on these measures, correlation analyses failed to produce significant results (all *r*'s < .16, *p*'s > .24). For a full list of correlation values for these analyses, please refer to Appendix E, Table 2. Thus, MI participants who experience worse or more frequent symptoms—or had experienced them for longer—did not show unusually prolonged or elevated sympathetic arousal, nor blunted parasympathetic function after stressor offset. One exception is the relatively interesting finding that MI participants who reported an earlier age of onset for their migraines tended to show more delayed and flatter PEP recovery curves as indicated by significant correlations between age of onset and α (r = .38, p = .04) and β (r_s = -.37, p = .03) recovery parameters.

3.8.2 Sensitivity Analyses Using Continuous Time Series as a Dependent Variable

It is possible that group differences in the time course of recovery and/or habituation within incongruent blocks were masked by averaging activation across epochs of interest. To explore whether there were any group differences in the time-course of SCL and HRV response within Incongruent and Recovery periods, additional group comparisons (*t*-tests) were conducted across all time-points of the stressor and recovery periods. To control for Type I error, all findings were subjected to temporal contiguity thresholds, which only focused on elevations in activation that persisted for a significantly long duration; only intervals significant at $p < .05$ are reported on here. For SCL analyses, 11 and 53 consecutive significant time-points were required for incongruent and recovery periods, respectively, to infer significance for the interval[23]. For HRV

[23] The mean autocorrelation for SCL time-series was .89 for incongruent periods and .94 for the recovery period.

analyses, the number of required consecutive time-points was 16 and 27 for incongruent and recovery periods, respectively[24].

Plots of mean time-series for MI and HC groups are presented in Figures 9-12.[25] To hold the scale of Y-axis consistent with values reported in primary analyses, these plots contain actual activity values; analogous plots of baseline-corrected activity for both measures can be found in Appendix D. Results of these analyses upheld findings from preliminary analyses of period means: SCL activity for MI and HC groups generally failed to differ significantly. As shown in Figure 9, there were no significant group differences in second-by-second SC at any of the time points across incongruent periods (*p*'s = .58-.99). Both groups showed a pattern of apparent within-block habituation during Incon1, with little to no apparent habituation within Incon2 and Incon3 blocks. As shown in Figure 10, HC and MI groups did not differ significantly in SCL at any time point across the 5 minute recovery period (*p*'s = .58-.90), and both groups showing a similarly shaped recovery curve.

[24] Mean autocorrelation for HRV was .98 for incongruent periods and .94 for the recovery period.
[25] Values used in these analyses consisted of change scores from baseline at each time point. Group comparisons using actual (e.g., raw) reactivity levels produced very similar plots with a slightly different scale, and no significant group differences.

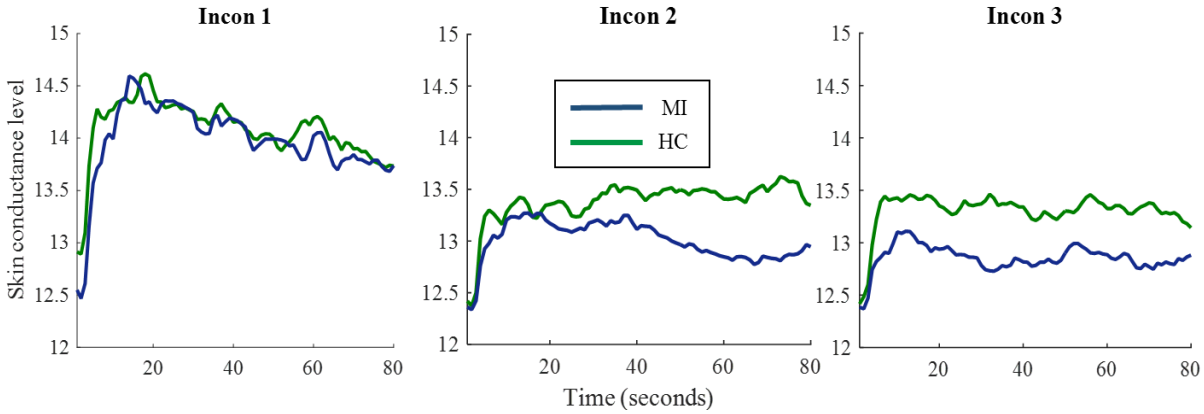

Figure 9. Mean skin conductance levels for migraineurs (MIs) and controls (HCs) across incongruent stressor blocks.

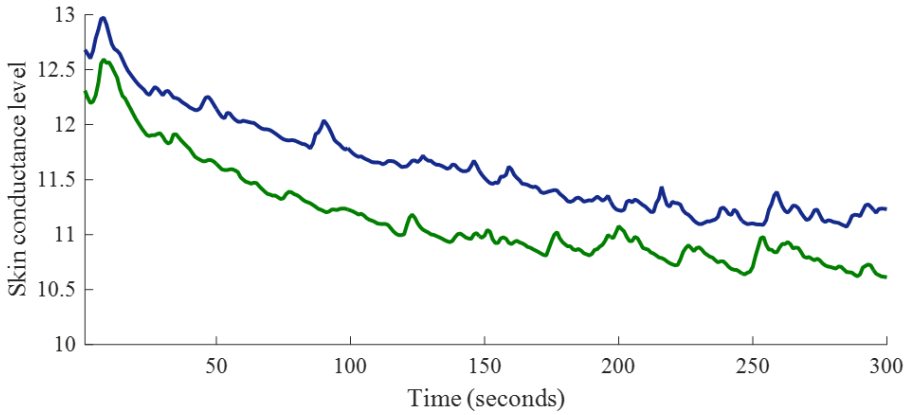

Figure 10. Mean skin conductance levels for migraineurs (MIs) and controls (HCs) during the post-stress recovery period.

As shown in Figure 11, both groups showed a characteristic suppression of HRV across all three incongruent blocks, suggesting vagal withdrawal persisted despite the repetition of the stressor. Second-by-second time-series comparisons revealed sharp decreases in HRV at the onset of each stressor period, with the most prominent differences between groups beginning almost immediately and persisting for approximately the first quarter to third of the task block (Incon 1: 9 to 30s, $t(66) = -2.54$, $p = .01$, $d = -.65$; Incon 2: 12 to 35s, $t(66) = -2.43$, $p = .02$, $d = -.60$; Incon 3: 6 to 28s, $t(66) = -2.80$, $p = .01$, $d = -.70$). Subsequently, both groups show a

gradual, parallel increase in HRV until the sharp uptick seen ~5 to 10s before the block ends, indicating the initiation of vagal rebound.

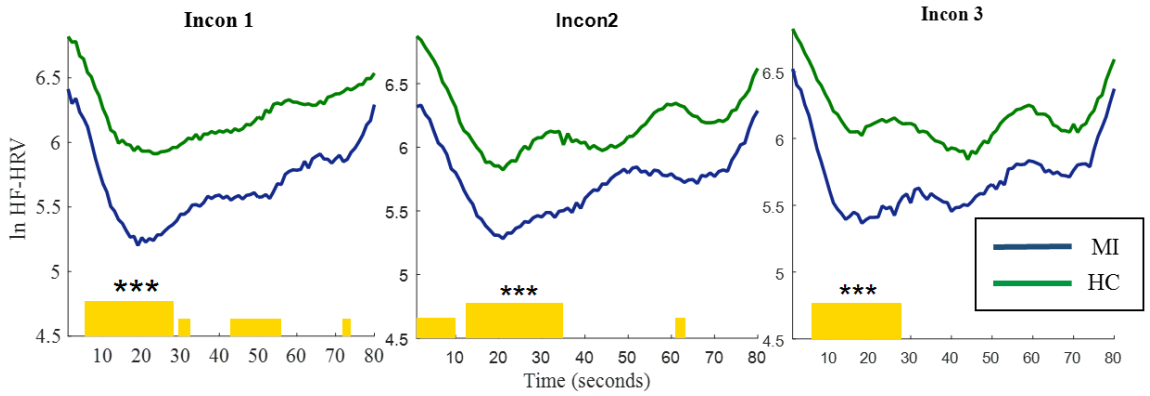

Figure 11. Mean heart rate variability (ln HF-HRV) for migraineurs (MIs) and controls (HCs) across incongruent stressor blocks. Yellow rectangles marked with asterisks denote periods for which the migraineurs and controls differed significantly and for a significant duration as defined by temporal contiguity thresholds[26]. To illustrate the function of thresholding procedures, additional time points where single comparisons were significant at p <.05 are denoted with smaller yellow markers; however only those windows marked with asterisks should be interpreted for the present results.

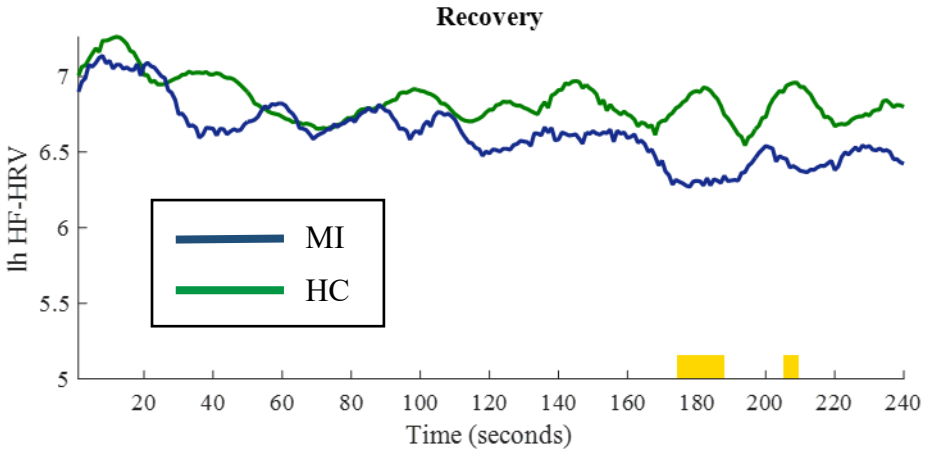

Figure 12. Mean ln HF-HRV for migraineurs (MIs) and controls (HCs) during the post-stress recovery period. Values represent change from baseline Yellow rectangles mark points at which p<.05; however, no temporal windows long enough to be considered significant based on temporal contiguity thresholding.

[26] See subsection 2.7.4.3 in the Methods for a description of temporal contiguity thresholding procedures.

Table 18

Correlations of Recovery and Habituation Variables with Proposed Covariates

Measure	*N*	Age[a]	BMI	SES student◊	Sleep (hours)	Caffeine load	Stress (PSS)	PROMIS Anxiety	PROMIS Depress.	7 Up Mania
SCL										
SCL habituation (Incon1-Incon2 slope)	65	**-.25***	-.004	-.001	-.05	.20	-.17	-.02	.08	-.1
SCL recovery (α parameter)[a]	61	-.02	.11	.20	-.09	.13	.07	-.18	-.23	.13
SCL recovery (β parameter)[a]	61	.22	.17	-.25	.05	.11	-.07	-.08	-.05	-.11
SCL recovery (Height parameter)	61	.08	.03	-.20	-.07	.09	.08	.09	.19	.02
PEP										
PEP habituation (Incon1-Incon2 slope)	67	.15	-.03	-.05	.20	-.21	-.12	-.1	-.07	.04
PEP habituation (Incon1-Incon3 slope)	67	**-.26***	-.11	.02	.05	-.14	-.09	-.04	-.07	.02
PEP recovery (α parameter)	62	-.02	-.08	.24	.01	-.05	-.05	-.11	**-.34****	-.01
PEP recovery (β parameter)[a]	62	.07	.03	-.28	.19	-.10	.03	-.12	.01	-.16
PEP recovery (Height parameter)	62	-.07	-.06	.14	**.28***	-.17	-.18	-.08	-.15	-.03

4.0 DISCUSSION

Psychological stress is the most widely reported trigger for migraines, and migraine sufferers are often considered to be particularly "stress sensitive;" however, only a few empirical studies have demonstrated clear evidence of physiological stress hyper-reactivity in this population. Given the number of theories implicating autonomic dysfunction in migraine, the centrality of the ANS in modulating stress response, the predominance of emotional stress as a migraine trigger, and the often lagged time course of headaches following stress, the investigation of sustained autonomic reactivity in migraineurs seemed like a logical next step.

The main goal in the present study was to replicate limited but promising findings of impaired physiological habituation to and recovery from stress in migraine sufferers (e.g., Coppola, Di Lorenzo, Schoenen, & Pierelli, 2013; Passchier & Orlebeke, 1983) using a repeated intermittent stressor task design and separate measures of SNS and PNS function. In addition, since psychological responses to stress could potentially interact with or amplify these physiological response patterns, a second goal was to determine whether individual differences in stress-related cognitive variables (e.g., stress appraisal and perseverative cognition) could help explain some of the observed abnormalities in autonomic responses. Consequently, our secondary aims rested heavily on the expectation that one or both of these patterns would be present in our sample. Results for primary analyses examining recovery and habituation were largely unsupportive of our original hypotheses, limiting our ability to test secondary aims.

There were no significant differences between groups in terms of their sympathetic habituation to or recovery following the stress task, and MIs did not show decreased vagal rebound, relative to controls, following stressor task offset. Surprisingly, however MIs *did* demonstrate a clear pattern of altered parasympathetic function during the stressor task itself, in the form of greater vagal withdrawal than HCs across all Incongruent blocks. As these results were not hypothesized, interpretations of these findings are henceforth offered cautiously; however, given the relative dearth of research on acute vagal withdrawal in the migraine literature, the following sections will offer alternative hypotheses and work to address the lack of hypothesized findings.

In the present study of female undergraduates, HCs and episodic MIs showed mostly comparable patterns of sympathetic recovery following stressor cessation, as well as largely indistinguishable patterns of sympathetic habituation to repeated intermittent stressor blocks. These results are in contrast with those of previous studies reporting elevated sympathetic arousal in migraine samples relative to controls during post-stress recovery and adaptation to prolonged or repeated stressors (e.g., Huber et al., 2005). As described previously, careful examination of the measures used in these studies does reveal that many group differences have been found in more general cardiovascular responses, such as diastolic blood pressure (Huss et al., 2009; Stronks et al., 1998), heart rate (Holm, Lokken, et al., 1997) or blood volume pulse (Hassinger et al., 1999b; Huber et al., 2005). While many of these findings were interpreted as "delayed sympathetic hyperarousal" or "sympathetic overactivity," few included direct measures of sympathetic input. Notable exceptions to this pattern include a number of studies that have used SC to demonstrate prolonged sympathetic recovery and poor adaptation to ongoing stressful stimuli (Cohen et al., 1978; Hassinger et al., 1999b; Holm, Lamberty, et al., 1997; Huber et al.,

2005). Such a pattern would make sense given evidence that migraineurs have diminished electrocortical habituation to repeated presentations of noxious stimuli (Ambrosini & Schoenen, 2003). It may be the case that the sympathetic system in isolation is not specifically affected in migraineurs, or that these abnormalities do not affect migraineurs' immediate responses to psychological stress. More generally, it may be important to consider whether separate and relatively "pure" measures of sympathetic output, like the ones used in this study, are truly the ideal measures on which to capture such differences.

In addition, it is possible that the lack of significant findings for the primary aims in the present study is due to methodological issues. One major concern across all laboratory stress studies is whether the chosen stressor task is sufficient to induce significant subjective stress and accompanying physiological changes. One could argue that the Stroop task used in the present study was simply not stressful enough to evoke meaningful changes in physiology; however, data from a number of indices would seem to suggest otherwise. For instance, results of preliminary analyses showing significant changes in all three autonomic measures (SCL, PEP, and HRV) in response to the task across groups would not support this argument. In addition, concordant self-report measures indicated that participants reported subjective task-related increases in anxiety and frustration in response to our stressor task. Thus, it is unlikely that we failed to detect group differences due to insufficient emotional and physiological responses to the task.

Furthermore, though MIs largely did not differ from HCs on sympathetic measures of stress response, they did differ with respect to parasympathetic stress reactivity (e.g., vagal withdrawal). While both groups of participants in the present study show clear vagal withdrawal from baseline, MIs showed a larger and more rapid suppression of vagal tone. As the proverbial

"fight or flight" system, the SNS tends to get most of the focus when discussing acute stress reactivity. Despite this, vagal withdrawal is a key feature of the stress response.

Pharmacologically-induced vagal withdrawal (e.g., elicited vagal blockade using atropine) has traditionally been used in establish individual differences in cardiac vagal tone, which has been linked to a number of important health outcomes. With respect to psychophysiological assessment, vagal withdrawal has been elicited using a variety of challenging laboratory stress tasks. Although traditional fear-inducing tasks, such as shock avoidance, are most recognized for inducing vagal withdrawal as part of a generalized response to environmental threat (Friedman, Thayer, & Tyrrell, 1996), other kinds of psychologically aversive tasks, such as timed arithmetic tasks and/or vigilance tasks, have been also shown to elicit vagal withdrawal fairly reliably. The modified Stroop task used in the present study had a combination of elements from both of these types of task designs, including a load buzzer that added an element of uncontrollability and, according to at least one participant, punishment.

Patterns of suppressed PNS function during cognitive activities, like worry, have been reported in other clinical populations considered to be particularly stress-sensitive and/or have difficulty disengaging from stressors. This has included panic-prone individuals (Berntson & Cacioppo, 2004) and patients with generalized anxiety disorder (Thayer, Friedman, & Borkovec, 1996) or functional pain conditions, such as fibromyalgia. Prolonged vagal withdrawal—along with threatening appraisals of physical symptoms—has also been implicated in the development of visceral hypersensitivity in Irritable Bowel Syndrome (Naliboff et al., 2006).

In the context of available information from the present study, it would be speculative to posit such a prominent role for vagal withdrawal as a mechanism in the stress-migraine relationship. In light of a growing recognition for the role of stress-related PNS hypofunction in

other stress-, anxiety-, and pain-related conditions, the present study's findings at least highlight the need to conceptualize the PNS more broadly in the context of the stress response. Though it has known functions that are important for relaxation and recovery from stress, more information is needed about the specific role it plays in the presence of acute (and repeated) stress.

The secondary aims of the present study concerned two cognitive variables that are potentially relevant to both acute and sustained physiological stress responses: stress appraisal and perseverative cognition. This was the first known study to directly investigate the construct of perseverative cognition in migraineurs. Given previous findings suggestive of sustained emotional reactivity in individuals with migraine, it was hypothesized that episodic migraineurs would report higher levels of trait (e.g., worry and rumination) and state perseverative cognition. Our results showed comparable levels of self-reported trait perseverative cognition in MIs and HCs. Curiously, on a measure of state perseverative cognition, MIs reported *lower* levels of task-unrelated perseverative thoughts following the laboratory stressor task, though they did not differ from HCs in terms of perseverative thinking about the stressor itself. Subsequent comparison of task-unrelated thoughts during baseline and recovery periods revealed that almost all participants experienced decreases in task-unrelated thought during the latter period; however, MIs experienced greater decreases than HCs.

This unexpected finding is challenging to interpret—particularly given the fact that MIs did not report thinking more about the task itself. What were they thinking about? One possibility, based on the literature, is that migraine sufferers were more focused on their present bodily state. Relative to controls, migraineurs have been shown to experience higher rates of subjective pain and physical tension in response to cognitive stressors presented in laboratory protocols (Stronks et al., 1998), and this has been interpreted as contributing to patterns of stress

somatization seen in chronic and episodic migraine (Huber & Henrich, 2003). The suggestion that episodic migraineurs are people who respond to stress by attending to bodily sensations and, in a sense, "feeling more pain" echoes previous (unpublished) work by this author that identified a similar pattern in the literature on adolescents with functional pain conditions.[27]

We predicted that stress appraisal would moderate the relationship between migraine status and habituation rate. In particular, we hypothesized that migraineurs who appraised stressors (and/or their ability to handle them) more negatively would have reduced sympathetic habituation relative to controls and migraineurs who made less negative appraisals. This hypothesis was built upon previously-reported associations between appraisal and habituation in healthy samples (Kelsey, Soderlund, & Arthur, 2004; Tomaka et al., 1993), as well as experimental and naturalistic evidence that heightened stress or threat appraisals are associated with a higher likelihood of subsequent headaches in migraineurs but not in controls (e.g., Kröner-Herwig et al., 1993). Ultimately, however, appraisal did not appear to moderate the migraine stress-habituation relationship, with the exception of one statistically marginal finding showing PEP habituation for HCs (but not MIs) depending on how threatening they perceived the task to be. This was particularly unexpected given evidence that appraisal can affect habituation and previously discussed associations between appraisal and the temporal sequence of stress-related migraines (Lokken, Holm, & Myers, 1997). In addition, we also proposed to examine whether individual differences in trait and state perseverative cognition could help

[27] This review and synthesis of studies comparing adolescents with functional pain to healthy controls produced the following relevant conclusions: a) adolescents with primary headache and other functional pain conditions may respond to threats/stressors by feeling pain; b) this process may involve differences in real or perceived physiological responses to threats; and c) individuals who report high emotional reactivity to pain also report high emotional reactivity to social threats and daily stressors.

explain any observed group differences in autonomic recover. As no group differences were detected for recovery variables, this hypothesis could not be tested.

Of note, MIs unexpectedly reported higher levels of state threat appraisal than did HCs in this study. This is in line with previous findings of more negative appraisal of stressors in migraineurs (Ehde & Holm, 1992), although this pattern has not always persisted in laboratory settings (e.g., Hassinger et al., 1999a). In addition to formal measures of threat appraisal, it is worth noting that MIs in the present study rated their feelings of stress and anxiety as significantly higher than HCs in anticipation of stressor task completion. It is unfortunate that physiological recordings were not taken during the stressor task training or during the period in which participants were answering these questions.

At least one take-away from the present study's findings in the area of stress-related cognitive variables is the value of state over trait-self-report measures in this population. Previous studies that have used only trait measures of stress reactivity have failed to find significant differences between migraineurs and controls on measures of stress appraisal, as well as other traits indicative of stress sensitivity (Gunel & Akkaya, 2008; Stronks et al., 1999). In contrast, several previous studies that used state measures of these variables did indeed find more negative stress appraisals and prolonged psychological reactivity to stress in migraine sufferers (Abbate-Daga et al., 2007; Holm, Lokken, et al., 1997; Stronks et al., 1999).

In addition to state self-report measures, MIs in the present study also reported that their lives felt significantly more stressful in general over the past two weeks. These findings, though unexpected, would seem to support previous claims that migraineurs are particularly "stress-sensitive" individuals (e.g., Hedborg et al., 2011). Interestingly, others have reported that migraineurs in general—and female migraineurs in particular—tend to report significantly higher

levels of trait stress susceptibility in the presence of more recent negative events; the same pattern does not seem to occur in headache-free controls (Hedborg et al., 2011; Houle et al., 2012). However, this did not seem to hold in the present sample, where perceived life stress was very high (particularly in MIs), and yet HCs and MIs reported comparable levels of stress-relevant traits such as threat appraisal and worry.

In addition, several ancillary findings indicated that migraineurs also differed in their subjective cognitive and emotional responses to the stressor task, in particular perceiving it as more threatening and feeling generally more anxious in anticipation of completing it. It is possible that other, in addition to acute biological stress responses, less straightforward mechanisms contribute to prolonged psychological stress response in migraine. For instance, several studies have postulated that migraineurs show maladaptive cognitive and behavioral reactions to real-life stressors, such as catastrophizing, social withdrawal, sleep disruption, and fixation on physical symptoms (Hassinger et al., 1999a; Houle et al., 2012; Huber & Henrich, 2003; Stronks et al., 1999). If this is the case, it is perhaps unsurprising that MIs in our sample reported higher levels of depression than HCs. Based on clinical and prospective epidemiological research, migraineurs tend to show a characteristic developmental pattern in which children presenting with anxiety go on to develop migraines, often in adolescence, followed by periodic depressive episodes in adulthood (Merikangas et al., 1990).

The lack of concordance between elevated subjective stress and anxiety in the absence of increased objective sympathetic arousal is a pattern that has been frequently reported in social anxiety disorder. Individuals with social anxiety continue to report subjective elevations in arousal (often accompanied by physical symptoms of anxiety), while showing normal decreases in physiological arousal indicative of normal habituation and recovery (Mauss, Wilhelm, &

Gross, 2003). Analogous findings have been reported in other anxiety disorders as well, particularly panic and generalized anxiety disorder; and in college females with high levels of functional somatic symptoms (Houtveen, Rietveld, & de Geus, 2003). Such findings have been interpreted by researchers as a demonstration of patients' attentional biases towards interoceptive cues, creating perceptions of anxious arousal—accompanied by greater subjective stress ratings—despite objective deceases in sympathetic arousal (Anderson & Hope, 2009; Mauss et al., 2003). Given previous reports of stress-reactive pain increases in migraineurs (e.g., Leistad, Sand, et al., 2007), the possibility of finding similar abnormalities in migraineurs' somatic experience of stress could be particularly helpful in differentiating incidental findings of greater (or less) objective arousal in migraineurs from more systematic alterations in subjective arousal. Furthermore, given a small but growing number of studies linking PNS hypofunction with elevated somatic symptoms and/or elevations in subjective anxious arousal in traditionally "stress sensitive" individuals, this could be a promising avenue to explore in future empirical studies.

A growing literature that supports the role of variables, such as self-efficacy and internal locus of control, in predicting clinical outcomes in the treatment of migraines (Nash & Thebarge, 2006). According to several authors, the degree to which participants perceive themselves as having control over their own physiological and emotional *response* to stress may be more central to primary headache pathology than the responses themselves (Martin & MacLeod, 2009; Nash & Thebarge, 2006). The more a headache sufferer feels capable of handling stressors effectively, the lower the observed association between stress and subsequent headaches (Marlowe, 1998).

Particularly relevant to this pattern is the use of biofeedback as an increasingly successful modality for treating migraine. If migraineurs truly do not show abnormally sustained elevations in autonomic arousal following stress, it is perplexing that biofeedback training—particularly protocols that target autonomic function—are proven to be so efficacious for migraine. The most commonly supported protocols teach patients to actively increase HF-HRV by engaging in certain types of paced breathing, and to decrease sympathetic arousal using a variety of strategies, often after intentional "stress inductions." At face value, the ability to decrease ongoing sympathetic responses and increase parasympathetic tone would seem to be the crucial active ingredients in these treatments and should, in theory, mediate decreases in headache frequency, severity, and related disability. However, with respect to clinical outcomes, psychological factors such as perceived self-efficacy again appear to explain much of the variability in outcomes between patients (Ellertsen et al., 1987; Gass & Glaros, 2013).

In an effort to minimally impact physiological recordings during and after the stress protocol, the present study made relatively sparse use of ongoing state self-report measures. However, ideal future stress protocols comparing migraineurs with controls might benefit from a more comprehensive assessment of ongoing sympathetic arousal, alongside state ratings of subjective stress, threat appraisal, pain, and/or subjective arousal symptoms, as well as continuous concurrent measures of parasympathetic function.

Additional methodological limitations should be noted. The generalizability of our findings is limited by the general racial and economic homogeneity found in our sample. These are particularly important factors when studying migraine or stress, as both tend to differentially affect individuals from various racial/ethnic groups and SES brackets. Relatedly, a major error in the preparation of self-report questionnaires led to almost a third of the sample missing SES data.

Based on the small effect sizes observed for associations with variables like sympathetic recovery parameters, it is possible that significant relationships would have been found with these variables had SES data been collected for the full sample.

With respect to the MI group used in the present study, the average participant experienced approximately two headache days per month, with the lowest frequency participants experiencing one headache a day every two months. Most of the previous studies reporting decreased physiological recovery have utilized samples with a higher cutoff for migraine frequency. Here, we attempted to make up for this by subsequently examining associations between migraine frequency and primary physiological outcome variables, but if group differences are truly only observable in instances of more chronic migraineurs, the sample we used was likely insufficient.

It is also possible that group differences between migraineurs and headache-free controls only emerge later in the course of migraine pathophysiology. The age of the present sample could be too young to fully represent the types of stress responses seen in individuals who have struggled with recurrent headaches for longer periods. In addition, although we attempted to control for the effects of hormonal fluctuations on stress response, we used a subjective report measure of menstrual phase to schedule participants. Such measures have been shown to be less reliable than previously thought (Sit, Seltman, & Wisner, 2011), and objective assays of follicular phase could be helpful in better controlling for this in future studies.

Our study sought to build upon a small but growing body of research showing sustained elevations in autonomic arousal in migraine sufferers, in the form of decreased habituation to stressors over time and prolonged recovery after stressor cessation. Thus, in the present study, we compared patterns of sympathetic and parasympathetic recovery and sympathetic habituation

in episodic migraineurs and non-headache controls using a repeated intermittent cognitive stressor task. We also explored relationships between physiological recovery and habituation and state and trait cognitive responses to stress, including stress appraisal and perseverative cognition. Our findings highlight, among other things, the need for increased flexibility in our conceptualization and measurement of autonomic stress responses, and in particular parasympathetic responses during acute stress. Further, they highlight the need to better understand associations between both objective and subjective (e.g., perceived) physiological stress responses. To build on this initial attempt to understand the pathophysiology of migraineurs' responses to stress, future studies can investigate the role of dynamic changes in state reports of pain, arousal, and stress appraisal, and how and when they covary with fluctuations in sympathetic and parasympathetic function.

APPENDIX A.

ADDITIONAL STROOP TASK BEHAVIORAL DATA

Table A1.

Emotion Ratings at Baseline, Pre-Stressor, and Post-Recovery for Groups

	Stressed	Mean Ratings ± SD		Period effect			Group effect			Group x Period effect		
Emotion	**Time**	**HC**	**MI**	**F**	***p***	**η_p^2**	**F**	***p***	**η_p^2**	**F**	***p***	**η_p^2**
Stressed	Baseline	2.26 ± 1.05	2.55 ± 1.15	.78	.46	.01	2.55	.12	.04	**4.70***	**.011***	**.07**
	Pre-stressor	**2.00 ± 1.02***	**2.76 ± 1.23***									
	Post-recov	2.24 ± .92	2.30 ± 1.16									
Frustrated	Baseline	1.35 ± .69	1.34 ± .75	**26.51***§	**<.001***§	**.29**	.39	.53	.01	.44	.64	.01
	Pre-stressor	1.97 ± 1.00	2.16 ± 1.08									
	Post-recov	2.06 ± 1.01	2.25 ± 1.24									
Anxious	Baseline	1.71 ± .76	2.15 ± 1.17	**16.18***§	**<.001***§	**.20**	3.27	.08	.05	3.00	.04	.04
	Pre-stressor	2.32 ± .98	2.97 ± 1.10									
	Post-recov	2.21 ± 1.07	2.24 ± 1.12									
Tired	Baseline	2.74 ± .99	2.82 ± 1.10	2.27	.11	.03	.09	.77	.00	.88	.42	.01
	Pre-stressor	2.59 ± 1.21	2.82 ± 1.36									
	Post-recov	3.00 ± 1.08	2.91 ± 1.26									

Note: HC=health controls; MI=migraineurs. *Significant at Bonferroni-corrected α level of .0125. §= Significant at Bonferroni-corrected α level of .0167. (.05/3 for three time points)

APPENDIX B.

PRIMARY RESULTS WITH PARTICIPANTS BMI ≤ 30

Table B1.

Baseline Values for Cardiovascular Variables by Group

Measure	HC Mean	MI Mean	Comparison
PEP	114.89 (8.19)	115.32 (7.93)	$t(61) = -.22$, $p = .83$, $d = -.06$
ln HF-HRV	6.42 (.64)	6.21 (.83)	$t(61) = 1.10$, $p = .27$, $d = .28$

Note: HC=health controls; MI=migraineurs; PEP=pre-ejection period; ln HF-HRV= high-frequency heart rate variability (natural log).

Table B2.

Reactivity Values for Cardiovascular Variables by Group

		Group Means		Inferential statistics		
Measure	**Period**	**HC**	**MI**	**Period effect**	**Group effect**	**Group x Period effect**
PEP	Baseline	114.88 ± 8.19	115.32 ± 7.93	F (1.55, 94.56) = 48.31, p <.001**, η_p^2 = .44	F (1, 61) = .01, p = .92, η_p^2 = .000	F (1.55, 94.56) = 5.69, p = .56, η_p^2 = .01
	Incon1	107.91 ± 10.10	108.04 ± 8.34			
	Incon2	110.97 ± 9.30	110.06 ± 7.83			
	Incon3	111.97 ± 8.91	111.74 ± 8.56			
ln HF-HRV	Baseline	6.42 ± .64	6.21 ± .83	F (2.66, 162.03) = 16.36, p <.001**, η_p^2 = .21	F (1, 61) = 4.50, p = .04**, η_p^2 = .07	F (2.66, 162.03) = 2.07, p = .11, η_p^2 = .03
	Incon1	6.10 ± .93	5.43 ± 1.04			
	Incon2	6.02 ± .86	5.62 ± .97			
	Incon3	6.00 ± .95	5.55 ± 1.08			

Note: HC=health controls; MI=migraineurs; PEP=pre-ejection period; ln HF-HRV= high-frequency heart rate variability (natural log).

Table B3.

Sympathetic Recovery – Group Comparisons of Gamma Function Parameters

	Group Means		
Parameter	**HC**	**MI**	**Group Differences**
α (offset)	.024 ± .022	.025 ± .018	t(56) = -.18, p = .86, d = -.05
β (rise-decay)	(Med) 3477.74	(Med) 1008.81	U =332.0, z =-1.37, p =.17
Height	116.33 ± 6.44	116.20 ± 8.40	t(56) = .07, p = .94, d = .02

Note: HC=health controls; MI=migraineurs. N=58

Table B4.

Parasympathetic Recovery – Group Comparisons of Vagal Rebound

	Group Means		
Parameter	**HC**	**MI**	**Group Differences**
Total Vagal Rebound	1.17 ± .82	1.27 ± .87	$t(59) = -.49$, $p = .63$, $d = -.13$
Final Vagal Rebound	.84 ± .79	.94 ± .87	$t(59) = -.46$, $p = .65$, $d = -.12$

Note: HC=health controls; MI=migraineurs. *N*=58

Table B5.

Sympathetic Habituation – 2 x 3 ANCOVA with Baseline and Incon1 Reactivity as Covariates

Period effect	**Group effect**	**Period x Group effect**
F (1.78, 103.22) = 33.34, p <.001**, $\eta_p^2 = .37$	F (1, 58) = 1.21, $p = .28$, $\eta_p^2 = .02$	F (1.78, 103.22) = 1.18, $p = .31$, $\eta_p^2 = .02$

APPENDIX C.

LINEAR REGRESSIONS WITH GROUP X APPRAISAL INTERACTIONS

Table C1.

Linear Regression of Pre-Ejection Period Slope (Incon1-Incon3) on Group x Trait Threat Appraisal Interaction

		B	SE	B	*p*	R^2	ΔR^2	ΔF	Sig. ΔF
Step 1						.01	.01	.16	.85
	Group	-.28	.92	-.04	.77				
	Trait Threat Appraisal	-.02	.04	-.07	.60				
Step 2						.01	.01	.58	.45
	Group	-.26	.91	-.04	.78				
	Trait Threat Appraisal	-.12	.13	-.35	.38				
	Group x Trait Appraisal	.07	.09	.30	.45				

Note: *N* = 67

Table C2.

Linear Regression of Pre-Ejection Period Slope (Incon1-Incon3) on Group x Trait Challenge Appraisal Interaction

		B	SE	β	*p*	R^2	ΔR^2	ΔF	Sig. ΔF
Step 1						.01	.01	.16	.86
	Group	-.27	.92	-.04	.77				
	Trait Challenge Appraisal	.05	.09	.06	.61				
Step 2						.01	.00	.28	.60
	Group	-.29	.92	-.04	.75				
	Trait Challenge Appraisal	.01	.12	.01	.96				
	Group x Trait Appraisal	.10	.19	.09	.60				

Note: *N* = 67

Table C3.

Linear Regression of Pre-Ejection Period Slope (Incon1-Incon3) on Group x State Threat Appraisal Interaction

		B	SE	β	*p*	R^2	ΔR^2	ΔF	Sig. ΔF
Step 1						.23	.05	1.71	.19
	Group	-.66	.92	-.09	.34				
	State Threat Appraisal	1.32	.72	.23	.65				
Step 2						.27	.02	1.54	.22
	Group	-.74	.92	-.10	.43				
	State Threat Appraisal	2.51	1.19	.44	.04				
	Group x State Appraisal	-1.84	1.48	-.26	.22				

Note: $N = 67$

APPENDIX D.

BASELINE-CORRECTED TIME SERIES FOR AUTONOMIC RESPONSES

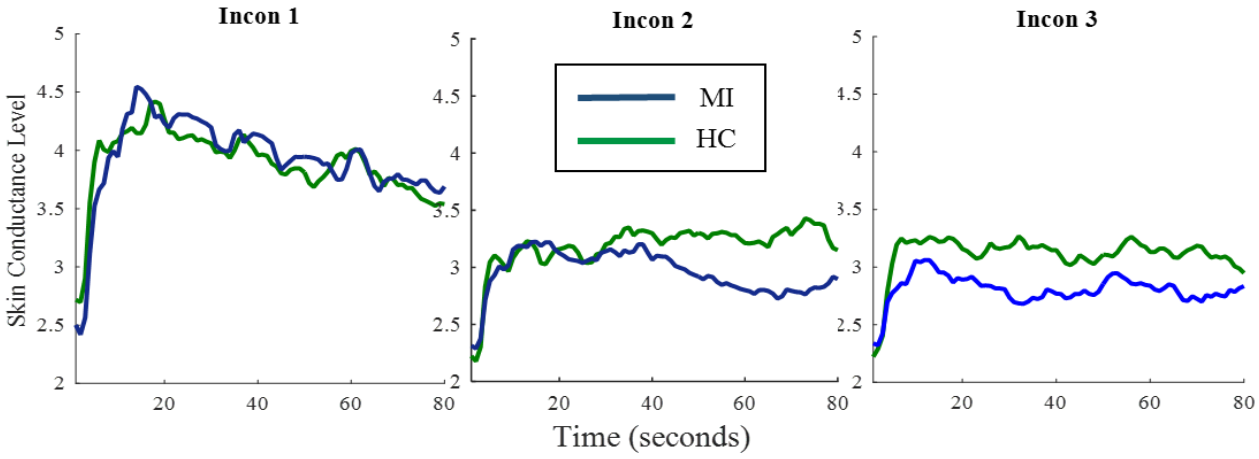

Figure D1. Mean baseline-corrected time series for SCL within incongruent periods for migraineurs and controls.

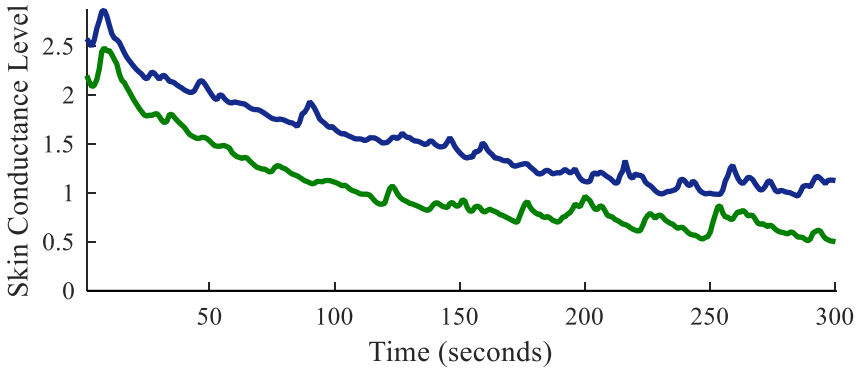

Figure D2. Mean baseline-corrected time series for SCL within the recovery period for migraineurs and controls.

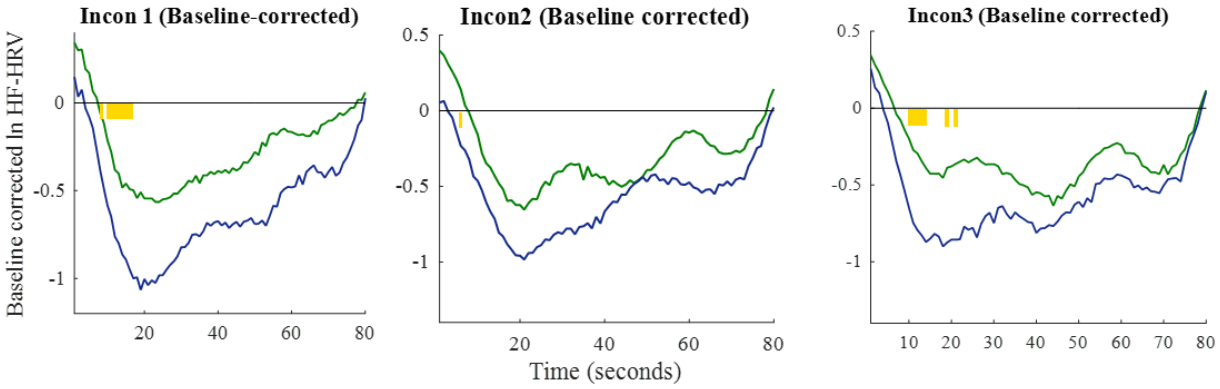

Figure D3. Mean baseline-corrected time series for ln HF-HRV across incongruent periods for migraineurs and controls.

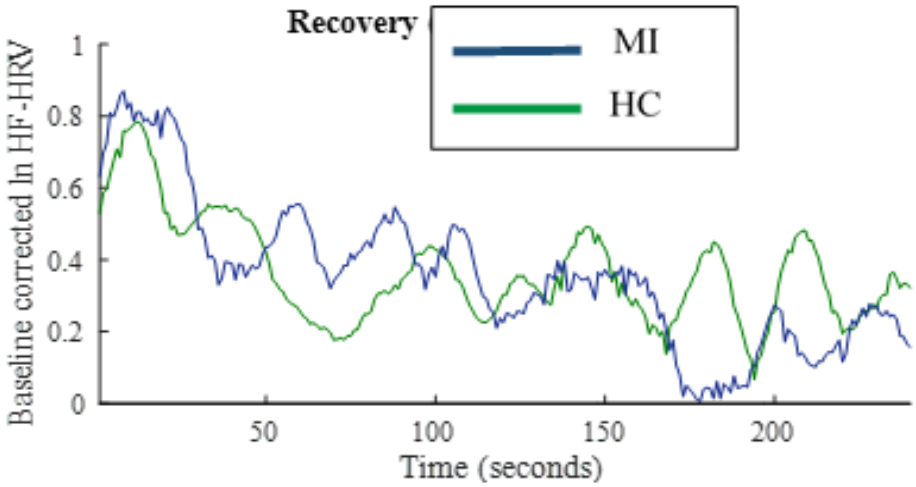

Figure D4. Mean baseline-corrected time series for ln HF-HRV within the recovery period for migraineurs and controls.

APPENDIX E.

ADDITIONAL CORRELATIONS FOR PHYSIOLOGICAL AND SELF-REPORT VARIABLES

Table E1.

Correlations Between Health-related Variables and Baseline Autonomic Function

Measure	**Health and self-report variables**						
	BMI	**SES student**	**Sleep (# hours)**	**Life Stress (PSS)**	**Anxiety Sx (PROMIS Anx)**	**Depression Sx (PROMIS Dep)**	**Mania Sx (7 Up scale)**
Baseline SCL	-.03	-.15	-.09	.02	.06	.08	.05
Baseline PEP	-.13	.33**	.11	-.03	.12	.04	.11
Baseline ln HF-HRV	.31*	-0.44**	-.02	-.02	.09	.10	-.14

Note: HC=health controls; MI=migraineurs; SCL=skin conductance level; PEP=pre-ejection period; ln HF-HRV= high-frequency heart rate variability (natural log). Significance of marked correlations: Baseline ln HF-HRV with BMI: $r = .31$, $p = .01$; Baseline PEP with SES student: $r = .33$, $p = .02$; Baseline ln HF-HRV with SES student: $r = -.44$, $p = .002$

Table E2.

Correlations Between Migraine Frequency and Severity Variables and Primary Autonomic Outcomes

Measure	N_{Total}	Migraine Freq[a] (MI + HC)	N_{MI}	Migraine Freq [a] (MI only)	Migraine Symptom Load	Age of Onset
SCL						
SCL habituation (Incon1-Incon2 slope)	65	-.09	31	.34	-.20	-.13
SCL recovery (α parameter)[a]	58	.08	29	.19	-.08	.06
SCL recovery (β parameter)[a]	58	.12	29	.04	.12	.11
SCL recovery (Height parameter)	58	.003	29	-.11	.30	.17
PEP						
PEP habituation (Incon1-Incon2 slope)	67	-.10	34	-.08	.25	-.07
PEP habituation (Incon1-Incon3 slope)	67	-.03	34	.01	.11	-.09
PEP recovery (α parameter)	63	.06	32	.02	-.22	**.38***
PEP recovery (β parameter)[a]	63	-.15	32	-.15	.16	**-.39***
PEP recovery (Height parameter)	63	-.07	32	-.02	.03	.06
ln HF-HRV						
ln HF-HRV peak vagal rebound	68	.12	33	.22	-.23	.09
ln HF-HRV final vagal rebound	68	.13	33	.18	-.05	.06

Note: HC=health controls; MI=migraineurs; SCL=skin conductance level; PEP=pre-ejection period; ln HF-HRV= high-frequency heart rate variability (natural log). * = p <.05; [a] = denotes measures for which Spearman's rho correlations were used due to non-normal distributions for one or both variables

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