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Examining the Efficacy of a Home-based Cognitive Behavioral Therapy Plus Capnometry-Assisted Respiratory Training for Persistent Post-Concussion Symptoms

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Examining the Efficacy of a Home-based Cognitive Behavioral Therapy Plus Capnometry-Assisted Respiratory Training for Persistent Post-Concussion Symptoms

A dissertation submitted in partial satisfaction of the

requirements for the degree of Doctor of Philosophy

in Psychology

by

Alexandra Sue Tanner

2021

ABSTRACT OF THE DISSERTATION

Examining the Efficacy of a Home-based Cognitive Behavioral Therapy
Plus Capnometry-Assisted Respiratory Training
for Persistent Post-Concussion Symptoms

by

Alexandra Sue Tanner
Doctor of Philosophy in Psychology
University of California, Los Angeles, 2021
Professor Michelle G. Craske, Chair

Persistent post-concussion symptoms (PPCS) extend well beyond the typical time course for concussion recovery and result in ongoing disability and suffering. For individuals who experience PPCS, little is known about what is causing their persistent symptoms and no gold standard treatment exists. The present study builds off the literature connecting autonomic nervous system (ANS) dysfunction and fear-avoidance to PPCS. In this study we propose a theoretical biopsychosocial model of PPCS and test the efficacy of a novel six-week home-based Cognitive Behavior Therapy (CBT) plus a biofeedback breathing training called Capnometry Assisted Respiratory Training (CART) for PPCS. We used a multiple baseline design (MBD) to examine treatment effects on avoidance, catastrophic thinking, ANS dysregulation, as measured

by $EtCO_2$ and pulse rate (PR), and post-concussion symptoms in a sample of 9 individuals with PPCS. MBD visual inspection and nonparametric randomization tests were used to examine changes in levels of activity engagement, pain catastrophizing and post-concussion symptoms between the baseline and treatment phases. Paired samples t-tests examined changes in a battery of self-report measures from pre- to post-treatment and at 6-weeks follow-up. Lastly multilevel mixed effects models examined how activity engagement, pain catastrophizing, $EtCO_2$ and PR changed over the course of treatment, and whether these changes mediated treatment effects on post-concussion symptoms. Results revealed significant reductions in post-concussion sleep symptoms and trend-level reductions in post-concussion physical symptoms from the baseline to treatment phase; significant reductions in behavioral avoidance and distress, pain catastrophizing, and illness-related beliefs from pre- to post-treatment that were maintained at follow-up; and significant reductions in pain catastrophizing and post-concussion physical symptoms during the treatment phase. Further, tests of mediation suggest that targeting pain catastrophizing may help to resolve physical symptoms of PPCS, although results must be interpreted with caution as the indirect effect did not meet statistical significance. Our findings provide support for a fear-avoidance model of PPCS and suggest that CBT may be beneficial for reducing avoidance, unhelpful injury- and pain-related cognitions, and post-concussion symptoms in individuals experiencing PPCS. Data collected during CART add to the literature of ANS dysregulation in PPCS by demonstrating hypocapnia at rest in most of our sample. Our findings have potential implications for identifying patients most likely to respond to CBT, helping patients with PPCS return to prior functioning and reducing the economic burden of PPCS by offering an accessible and scalable intervention.

The dissertation of Alexandra Sue Tanner is approved.

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Introduction

The present dissertation proposes a biopsychosocial model of persistent post-concussion symptoms (PPCS) and tests the efficacy of a novel home-based cognitive behavioral therapy (CBT) targeting the hypothesized underlying factors. The introduction will provide a brief background on PPCS followed by an overview of the literatures linking autonomic dysfunction and a fear avoidance model to PPCS. Next, we will review the existing literature of CBT for PPCS and introduce multiple baseline single case designs. Lastly, we will review the evidence for the cognitive behavioral interventions included in our novel home-based treatment and self-guided CBT, and define study aims and hypotheses.

In the United States an estimated 1.7 – 3.8 million traumatic brain injuries (TBIs) occur each year, of which 75-90% are classified as a mild traumatic brain injury (mTBI; Marin, Weaver, Yealy, & Mannix, 2014; Selassie, Wilson, Pickelsimer et al., 2013). Sports, motor vehicle accidents, falls, and military-related blast injuries are among the most common causes of mTBI (Haddany & Efrati, 2016). An estimated $56 billion is spent on health care costs of TBI each year in the United States, with mTBI/concussion comprising 44% of the total cost (e.g., Belanger, Spiegel, & Vanderploeg, 2010). Concussion is an mTBI caused by a force or impact to the head or body during which the brain moves back and forth quickly and results in neuropsychological symptoms or altered brain function. Altered brain function is defined as any of the following: any duration of loss of consciousness, loss of memory of events immediately before or after the injury, altered mental state at time of injury (e.g., confusion, disorientation), and neurological deficits (e.g., loss of balance, change in vision, sensory loss; Menon, Schwab, Wright, & Maas, 2010). TBI classification is determined by length of loss of consciousness and post-traumatic amnesia (i.e., longer lengths indicate more severe TBI) and uses the Glasgow

Coma Scale (GCS; Teasdale & Jennett, 1974), a 15-point scale assessing motor response, verbal response, and eye opening, to determine the level of consciousness directly after injury. Higher GCS scores reflect increased consciousness and TBIs are considered an mTBI if patients score between 13-15 (Friedland, 2013).

Following concussion, individuals often experience a combination of physical, sleep, emotional, and cognitive symptoms. These symptoms include headache, nausea, dizziness, difficulty with balance, sensitivity to light and noise, visual problems, fatigue, insomnia or hypersomnia, drowsiness, irritability, sadness, anxiety, increased emotionality, impaired concentration and memory, and feeling slowed down and mentally "foggy". In most individuals, symptoms resolve within 2-4 weeks (e.g., Ryan & Warden, 2003). A subset of individuals, however, report continued symptoms for months and sometimes years after injury (prevalence rates vary greatly depending on diagnostic criteria, population, time of assessment, etc.; Polinder et al., 2018). According to the National Athletic Trainers Association (NATA), concussions are expected to resolve within four weeks and athletes who are symptomatic beyond this time are considered to be outside the typical recovery window (Leddy, Baker, Haider, Hinds, & Willer, 2017). When symptoms persist longer than 2 – 3 months, they are classified as persistent post-concussion symptoms (PPCS). Some even suggest that PPCS should be considered as early as three weeks post-injury if symptom improvement is not present (Willer & Leddy, 2006).

Historically, the medical field has referred to PPCS as "post-concussion syndrome". The World Health Organization (WHO) International Classification of Disease-10 (ICD-10) defines post-concussion syndrome as the persistence of three or more of the following symptoms: fatigue, headache, dizziness, irritability, insomnia, concentration difficulties, or memory difficulties. However, there are limitations to classifying this condition as a "syndrome". A

syndrome suggests a homogenous presentation with shared pathophysiology. In actuality, there is vast heterogeneity in symptoms across patients following concussions. Further, ongoing research in the field suggests that the various phenotypic post-concussion presentations have different recovery trajectories and may reflect different underlying mechanisms (e.g.,Kamins et al., 2021). As such, attempting to classify all persistent post-concussion presentations as the same physiological condition may ignore meaningful clinical information and likely contributes to a less specific "one-size-fits-all" treatment approach. In recent years there has been a push in the field to reclassify post-concussion syndrome as PPCS to emphasize the persistence of symptoms, identify mechanisms underlying the various phenotypic presentations, and increase treatment specificity (e.g., McCrory et al., 2018).

Numerous clinical factors have been associated with increased risk of PPCS, such as history of prior concussions, history of cognitive dysfunction, history of depression or anxiety, female sex, and younger age (Leddy et al., 2017). Additionally, posttraumatic headaches with a migraine phenotype appears to be associated with a longer recovery time post-injury (Kamins et al., 2021). While these risk factors may help to identify individuals more likely to develop PPCS they do little to inform treatment targets to resolve or prevent PPCS. Further, persistent symptoms are associated with increased health care service use and disability (Kristman et al., 2014; Kirsch et al., 2010; Lundin, de Boussard, Edman, & Borg, 2006; King & Kirwilliam, 2011). Thus, identification of factors that contribute to PPCS and treatments to target those factors to reduce symptoms and help patients return to prior functioning are warranted.

Factors Contributing to PPCS

Autonomic Nervous System Dysfunction

Concussions have been described as a systemic injury that results in disturbance of physiological systems throughout the body (Leddy et al., 2007). Autonomic nervous system (ANS) dysfunction has been proposed as a potential factor contributing to PPCS. Alterations to autonomic functioning have been observed in individuals who have recently sustained a concussion (e.g., Leddy et al., 2017). Consistent with rates of concussion recovery, disruptions in physiological indicators of ANS dysfunction typically resolve in two to four weeks post-injury (Len & Neary, 2011). Among individuals with PPCS, ANS dysfunctions appear to be sustained.

The ANS plays a critical role in numerous regulatory systems in the body involved in everyday functioning and maintenance of adaptive responses to internal and external changes (Pertab et al., 2018). More specifically, the ANS is involved in regulating the sympathetic and parasympathetic branches of the ANS; innervates cardiac and smooth muscles and glands in organ systems throughout the body; regulates organ systems to respond optimally to changes in internal and external environment (e.g., temperature, light, increased threat) and changes in behavior (e.g., feeding, postural changes); regulates physical processes such as blood pressure, gastrointestinal movement and secretion, body temperature, and metabolism; regulates dilation and constriction of blood vessels; and maintains a balance of blood flow to the brain (i.e., cerebral profusion; Pertab et al., 2018). Given the involvement of ANS in many physiological processes, it is unsurprising that disruptions to ANS functioning may result in a cascade of cognitive, physical, and emotional symptoms.

Heart rate and end-tidal CO_2 ($ETCO_2$) are two non-invasive, portable and accessible measures of ANS functioning that have previously been found to be dysregulated in individuals with PPCS. Compared with non-concussed controls, individuals with concussions showed greater heart rate at rest (King, Lichtman, Seliger, Ehert, & Steinberg, 1997) and following

cognitive or exercise physiological stressors (Hanna-Pladdy, Berry, Bennett, Phillips, & Gouvier, 2001; Gall, Parkhouse, & Goodman, 2004). A study comparing female college athletes with PPCS to non-concussed gender-matched controls showed altered physiological response to exercise (Clausen, Pendergast, Willer, & Leddy, 2016). The literature on $EtCO_2$ in PPCS suggests elevated $EtCO_2$ during physical and cognitive exertion, however, the findings at rest are mixed. One study demonstrated that patients with PPCS had higher heart rate during exercise onset and elevated $EtCO_2$ throughout exercise during equivalent workloads compared to controls (Clausen et al., 2016). Another study found that $EtCO_2$ was higher in patients with PPCS at rest, while walking, and during a computerized test of neurological functioning (Immediate Post-Concussion Assessment and Cognitive Test; ImPACT) compared to non-concussed controls (Siedlecki, Sanzo, Zerpa, & Newhouse, 2018). A study by our group found that compared to healthy controls, individuals with PPCS had lower $EtCO_2$ levels at rest (Snyder et al., 2021). Conflicting results may be due to methodological differences and limitations of the study by Siedlecki et al. (2018). Specifically, Siedlecki et al. reported average $EtCO_2$ during a 20-second baseline versus a 5-minute baseline used by Snyder et al. which likely reflects a more stable and accurate measure of rest. Concussed individuals also showed a lower respiration rate interval during low-to-moderate exercise compared to controls, suggesting an exercise-induced uncoupling of the autonomic and cardiovascular systems (Gall et al., 2004).

Numerous assessment methods of ANS functioning have been explored in concussion-related research (Pertab et al., 2018). While the majority of research suggests that the ANS is disrupted following concussion and in PPCS, the field is limited by methodological variations between studies. According to a 2018 systematic review of the literature, no two studies have evaluated ANS outcomes using identical procedures, precluding meta-analyses and identification

of primary indictors of PPCS-related ANS dysfunction (Pertab et al., 2018). The present study aims to replicate prior findings demonstrating anomalies in heart rate and $EtCO_2$ among individuals with PPCS at rest and develop an intervention directly targeting these processes to normalize functioning and resolve post-concussion symptoms.

Fear Avoidance Model

A fear avoidance model has been proposed as an explanation for PPCS. A systematic review of multivariable prognostic models of mTBI suggest that both pre-injury mental health and post-injury anxiety predict PPCS (Silverberg et al., 2015). Individual symptoms reported by those with PPCS are not unique to concussions and overlap with both psychological conditions, including depression and anxiety, and bodily distress syndromes, such as chronic pain and migraine. In fact, "post-concussion like" symptoms were found in a sample of healthy controls at a prevalence rate comparable to that found in mTBI (Iverson & Lange, 2003). Additionally, in the sample of healthy controls "post-concussion like" symptoms were strongly correlated with depressive symptoms (Iverson & Lange, 2003). These findings suggest that PPCS may reflect underlying psychological factors.

Kay, Newman, Cavallo, Ezrachi, and Resnick first proposed a fear avoidance model of PPCS in 1992. Kay and colleagues (1992) proposed two cycles of avoidance that develop in response to PPCS which subsequently maintain symptoms. The authors identified both a 'subjective cognitive dysfunction loop' and a 'dysfunctional pain loop', in which following concussions patients experience cognitive deficits or pain which interfere with their ability to function, causing worries about their recovery and ability to cope or function, leading to anxiety and a tendency to avoid situations that exacerbate or reinforce cognitive deficits/pain, resulting in

depression, which further perpetuates cognitive deficits and pain, and so on. The authors proposed that classic PPCS is observed when both cycles occur in conjunction.

Post-concussion symptoms are common among individuals with other bodily distress syndromes, such as chronic pain (Iverson & McCracken, 1997). Further, the proposed 'dysfunctional pain loop' (Kay et al., 1992) is similar to the well-validated fear avoidance model of chronic pain which posits that long-term pain is maintained by a heightened threat-value of pain and avoidance of any activities that may exacerbate pain (e.g., Vlaeyen & Linton, 2012), lending support for a fear avoidance model underlying PPCS. Similarly, research on cogniphobia (i.e., the avoidance of cognitive exertion due to fear of headaches) and mTBI found that cogniphobia is associated with more severe headaches, poorer memory performance, and increased avoidance of other physical activities at two to three months post-injury (Silverberg, Iverson, & Panenka, 2017). These results suggest a negative reciprocal cycle, similar to the 'subjective cognitive dysfunction loop', whereby increased fear and avoidance of cognitive exertion maintain cognitive difficulties and pain following mTBI.

Wijenberg, Stapert, Verbunt, Ponsford, and Van Heugten (2017) recently conducted the first empirical test of a combined pain-cognition fear avoidance model in a sample of individuals with PPCS following TBI. The full sample included individuals who sustained mTBI (65% of sample) and more severe TBI, and analyses were run on both the full sample as well as the subset of individuals with mTBI. Results showed that 10% of all patients endorsed high levels of catastrophizing and 35% endorsed high levels of fear avoidance behavior. Among the subset of individuals with mTBI, 16% of patients endorsed high levels of catastrophizing and 27% endorsed high levels of fear avoidance behavior. Values were not significantly different between the full sample and mTBI subset. Results found that catastrophizing, fear avoidance behaviors,

depressive symptoms and post-concussion symptoms were all significantly correlated in both the full sample and mTBI subset. Albeit with lower rates of fear avoidance and catastrophizing than that found in other bodily distress syndromes, such as chronic pain, results suggest that the fear avoidance model contributes to PPCS. The authors discuss limitations of their study that may explain the lower rates of fear avoidance behaviors and catastrophizing, such as scale adaptations that may have reduced sensitivity and specificity of their measures (Wijenberg, Stapert, Verbunt, Ponsford, & Van Heugten, 2017). The present study will build upon preliminary evidence for a fear avoidance model of PPCS by examining avoidance behaviors and catastrophic thinking longitudinally in a sample of individuals with PPCS and assessing whether they mediate treatment effects on post-concussion symptoms.

Evidence for Psychological Interventions for PPCS

During the acute recovery phase of concussion most individuals are instructed to avoid strenuous physical and cognitive activity for the first two to five days post-injury, after which they are told to rest while resuming daily activities as soon as possible, and gradually reengage in physical and cognitive tasks as symptoms subside (Willer & Leddy, 2006). For the subset of individuals who do not experience the expected spontaneous remittance of symptoms within the first two to four weeks, no gold standard treatment exists. Many individuals continue to rest hoping for symptoms to remit, however, research suggests that while rest may be beneficial during the acute recovery phase, long-term rest may lead to physiological deconditioning, metabolic disturbances, increased fatigue, and depression (Willer & Leddy, 2006; Berlin, Kop, & Deuster, 2006). No empirical evidence exists supporting benefits of rest beyond a few weeks post-injury (Leddy, Sandhu, Sodhi, Baker, & Willer, 2012). In fact, an RCT recommending strict rest for five days versus usual care (i.e., rest for 1-2 days followed by gradual return to activity)

following concussion found that individuals in the strict rest condition reported higher daily post-concussive symptoms and slower symptom resolution (Thomas, Apps, Hoffmann, McCrea, & Hammeke, 2015).

Given the proposed theoretical models linking ANS dysfunction and fear avoidance to PPCS, cognitive behavioral therapy (CBT) represents a promising intervention. The current evidence base for CBT for PPCS is small and methodologically flawed but suggests potential benefits and encourages additional research. A recent systematic review of psychotherapeutic interventions for PPCS identified five studies, of which only two were randomized controlled trials (RCTs; Bergersen, Halvorsen, Tryti, Taylor, & Olsen, 2017). The review limited inclusion to studies conducted after 1994, on populations at least three months post-injury, and using psychotherapeutic interventions as defined by the American Psychological Association (APA, 2012). The type of interventions, treatment targets, and outcome variables varied for each study, with some studies aiming to reduce all post-concussion symptoms and others targeting specific symptoms (e.g., cognitive impairment).

The first RCT included in the review was conducted by Kjeldgaard and colleagues (2014) and used a waitlist-control design to examine the effects of a nine-week group CBT for chronic post-traumatic headache and was deemed the most methodologically rigorous of the studies reviewed (Bergersen et al., 2017). The CBT intervention followed a manual including psychoeducation on PPCS and the CBT model, cognitive restructuring to encourage a more active daily life, improve quality of life and reduce psychological stress, and relaxation techniques to reduce physical tension (Ferguson & Mittenberg, 1995). Results found a small benefit of CBT on quality of life but no effects on headaches and pain threshold (Kjeldgaard et al., 2014). Further, compared to the treatment group, individuals in the waitlist-group showed

significant reductions in somatic and cognitive symptoms, suggesting spontaneous remission. All group therapy sessions were led by the first author which may limit generalizability of results by potentially introducing bias or therapist effects. Bergersen et al. (2017) also point out that Kjeldgaard et al. (2014) did not assess adherence to the treatment or include intention to treat analyses.

The second RCT included in the review used a waitlist-control design to examine an 11-week (two 50-minute sessions per day, 3-times per week) combined manualized intervention of cognitive remediation and CBT for cognitive dysfunction and emotional distress (Tiersky et al., 2005). Results showed treatment improvements in emotional functioning and reduced anxiety and depression that were maintained at one- and three-month follow-up. Performance on an auditory attention task also improved following treatment. A limitation of the study is the time-intensiveness of the treatment, which may reduce scalability of the intervention. Due to the simultaneous delivery of CBT and cognitive remediation, unique effects of each intervention are unknown and we cannot conclude whether similar benefits could be yielded by CBT alone. Additionally, authors did not assess adherence to the manual or whether observed changes were clinically significant and did not conduct intention to treat analyses (Bergerson et al., 2017).

The remaining three studies included in the Bergersen et al. (2017) review utilized less rigorous designs, including an AB single case design, non-randomized case control design, and an open trial (Waid-Ebbs et al., 2014; Azulay, Smart, Mott, & Cicerone, 2013; Riegler, Neils-Strunjas, Boyce, Wade, Scheifele, 2013). Bergersen et al. (2017) inaccurately described one study as a multiple baseline design rather than an AB single case design in which all participants completed the same 5-week baseline duration before receiving the intervention (Waid-Ebbs et al., 2014). Without the randomization to multiple baselines of varying length (or using a different

type of single case design, such as ABAB), we cannot be certain that improvements seen at the introduction of the intervention are a result of the intervention rather than the passage of time. Treatments varied across the three studies, including a metacognitive Goal Management Training (GMT; Waid-Ebbs et al., 2014), mindfulness-based stress reduction (MBSR; Azulay et al., 2013), and Military On-Line Problem Solving Videophone Intervention (MOPS-IV; Riegler et al., 2013). In general, the studies showed favorable results, including improvements in objective measures of executive functioning (Waid-Ebbs et al., 2014), self-report quality of life and self-efficacy, and some measures of memory and attention (Azulay et al., 2013), and performance on memory and learning tests (Riegler et al., 2013). An additional randomized waitlist-control trial conducted after the above systematic review found improvements in self-reported quality of life, as well as measures of anxiety and fatigue after controlling for treatment duration, after 12-weeks of an individual semi-structured CBT (Potter, Brown, & Fleminger, 2016). However, due to the individualized nature of the CBT intervention we cannot confirm whether individuals received the same intervention, further impeding replication (Potter et al., 2016).

Findings of the above studies should be interpreted with caution due to methodological limitations. Notably, a lack of adequate control groups in many of the studies make it difficult to draw conclusions about the efficacy of the interventions (Bergersen et al., 2017). Additionally, many of the interventions were delivered by a single therapist introducing potential bias or therapist effects. Further, previous CBT interventions were not tied to underlying theoretical models, such as a fear avoidance model. Despite these limitations, combined results suggest CBT may be a promising intervention for PCS. The present study will add to the existing literature by 1) proposing a theoretical model for PCS highlighting treatment mechanisms to increase specificity of CBT interventions and 2) developing a novel manualized home-based treatment to

target the proposed underlying mechanisms, which, if effective, could be easily replicated and disseminated.

Single Case Designs

Single case designs represent an ideal methodological design for clinical research. Similar to group designs, single case designs are true experiments that can demonstrate causal relations (Kazdin, 2003). Unlike group designs which are slow and require large sample sizes to detect group differences, single case designs are efficient and have robust power to detect significant effects with small sample sizes. Individuals serve as their own control which allows for the tailoring of treatments to meet individual needs (Dallery & Raiff, 2014). This design may be ideal for a condition like PPCS which is quite heterogeneous across individuals. Single case designs involve the daily assessment of dependent measures (often symptoms or behaviors) in individuals to monitor stability and changes over time. Four key characteristics of single case designs allow for causal inferences of the intervention: continuous assessment, baseline assessment, stability of performance, and use of different phases (Kazdin, 2003).

Continuous assessment is the most essential component of single case experiments and involves collecting repeated observations of the dependent measures (often daily) before and during the intervention (Kazdin, 2003). Continuous assessment provides data on the pattern and stability of the dependent measures and whether introduction of the intervention results in changes to levels of the dependent measures. Additionally, this data helps to inform decisions about when to change phases of the design. The second key characteristic is collecting a baseline assessment of the dependent measures prior to implementing the intervention (Kazdin, 2003). The baseline assessment serves two functions: 1) describing the level of the dependent measures before the intervention begins and 2) extrapolating a continuation of the baseline performance to

predict the level of the dependent measures in the immediate future without the intervention. The third key characteristic, stability of performance, allows for the extrapolation of baseline data to the immediate future to evaluate the effect of the ensuing intervention (Kazdin, 2003). A stable performance during the baseline ideally has little variability over time so that changes in slope are readily detectable after beginning the intervention. The final key characteristic of single case designs is the use of different phases (Kazdin, 2003). Design phases are periods of consecutive time (i.e., multiple days or weeks), such as the baseline or intervention, during which continuous assessment of the dependent measures occur. Multiple phases allow for comparison of patterns of the dependent measures as a result of the phase.

Multiple baseline designs are a form of single case design in which individuals are randomized to baselines of varying lengths prior to beginning the intervention phase. By varying the length of the baseline phase, investigators can attribute changes observed after implementing the intervention to the treatment rather than the passage of time (i.e., spontaneous remission; Kazdin, 2003). Multiple baselines require a minimum of two baseline durations, which allows for replication of an observed treatment effect (i.e., changes in the dependent measure only occur after the start of the intervention phase regardless of baseline length; Kazdin, 2003). Multiple baseline designs follow an AB design and are useful for interventions that involve learning (i.e., withdrawing or altering the intervention may not result in reversal of the dependent measures to baseline levels; Kazdin, 2003). An advantage of single case designs is the ability for response guided experimentation, however, because multiple baselines require randomization to the start of treatment regardless of performance, individuals may be randomized to begin the intervention prior to achieving a stable baseline. It is thus important to select dependent measures that remain stable over time or begin randomization after dependent measures have stabilized (Ferron &

Sentovich, 2002). Treatment effects are determined by graphing performance of the dependent measures and comparing the magnitude of the slopes over baseline and treatment phases, specifically noting the change in slope after treatment is implemented. Randomization tests are also performed to determine whether changes meet statistical significance.

Present Study

Evidence for CBT Treatment Techniques

The intervention developed for the present study utilized therapeutic techniques that have yielded significant reductions in avoidance behaviors and catastrophic thinking and normalization of ANS dysregulation in anxiety, depression, and bodily distress syndromes, including chronic pain.

Research in the fields of anxiety disorders and chronic pain identify exposure therapy as an effective intervention for reducing avoidance, symptom severity and improving quality of life (e.g., Carpenter et al., 2018; Leeuw et al., 2008; Woods & Asmundson, 2008). Exposure therapy involves repeatedly confronting feared and avoided stimuli to disconfirm overestimation of threat value and underestimation of one's resources or ability to cope. Exposure therapy, by nature, directly targets avoidance behaviors and encourages approach behaviors. Additionally, exposures provide individuals repeated opportunities to learn that feared outcomes are not as negative, extreme, or as likely to occur as previously believed. As such, exposure therapy is also effective in altering catastrophic thinking (e.g., Crombez et al., 2002). A study examining exposure to physical movements in individuals with chronic low back pain found that exposure helped correct overpredictions of pain in high catastrophizers (Crombez et al., 2002). A randomized controlled trial (RCT) comparing in vivo exposure treatment to operant graded activity for chronic low back pain in adults showed that exposure reduced pain intensity,

increased daily activity levels and improved functional disability and was significantly more effective than graded activity in reducing pain catastrophizing and perceived harmfulness of activities (Leeuw et al., 2008). Additionally, pain catastrophizing and perceived harmfulness significantly mediated effects of exposure therapy on functional disability and main complaints (i.e., degree of difficulty performing various activities; Leeuw et al., 2008). A second RCT comparing in vivo exposure to graded activity and a wait-list condition for chronic pain in adults found that exposure led to significantly greater improvements in fear of pain/movement, fear avoidance, pain-related anxiety, and pain self-efficacy compared to graded activity, and significantly greater improvements in fear avoidance beliefs, fear of pain/movement, pain-related anxiety, pain catastrophizing, pain experience, and anxiety and depression compared to wait-list control post-treatment, with improvements maintained at one month follow-up (Woods & Asmundson, 2008). A pilot study exploring the use of exposure and acceptance strategies to encourage values-driven approach behaviors for idiopathic chronic pain in adolescents found significant improvements in catastrophizing, pain, functional ability and school attendance post-treatment and at three- and six-month follow-up (Wicksell, Melin, & Olsson, 2007). Given the evidence supporting the use of exposure for reducing both avoidance behaviors and catastrophizing, the present study incorporated exposure in the treatment of PPCS.

Cognitive restructuring is a commonly used therapeutic technique to target maladaptive thinking patterns, such as catastrophizing. Cognitive restructuring involves identifying, challenging, and replacing inaccurate and catastrophic thinking to encourage more balanced and accurate thinking patterns and cognitive flexibility. A meta-analysis by Dobson (1989) examined the effect of cognitive therapy versus pharmacotherapy, behavior therapy, other psychotherapies, wait-list control, and no-treatment control for the treatment of depression. Results indicated that

cognitive therapy resulted in greater benefits for depression than comparator treatments (Dobson, 1989). In both clinical research and practice cognitive restructuring techniques are often combined with other treatment strategies (e.g., behavioral, relaxation), making it difficult to disentangle unique treatment effects. However, strong evidence exists for cognitive-behavioral strategies, including cognitive restructuring, in the treatment of depression and anxiety disorders in both adults (e.g., Beck, Emery, & Greenberg, 2005) and adolescents (e.g., Ishikawa, Okajima, Matsuoka, & Sakano, 2007; Reinecke, Ryan, & DuBois, 1998). A review of meta-analyses of randomized placebo-controlled trials of CBT for anxiety and related disorders in adults found that interventions using primarily cognitive strategies had comparable effect sizes to exposure strategies (Carpenter et al., 2018). Cognitive restructuring has also proven an effective strategy for reducing pain catastrophizing in bodily distress syndromes. An RCT examining the efficacy of CBT (cognitive restructuring and cognitive/behavioral coping) versus wait-list control on pain catastrophizing in adults with chronic headache showed that CBT significantly reduced catastrophizing and anxiety and increased self-efficacy compared to waitlist, with improvements maintained at follow-up (Thorn et al., 2007). No overall differences were found between treatment conditions in the reduction of headache frequency or intensity, however, 50% of individuals who received CBT showed clinically meaningful reductions in headache indices (frequency, intensity, unpleasantness of pain; Thorn et al., 2007). Cognitive restructuring strategies were included in the treatment manual of the present study to target catastrophic thinking, which may in turn encourage approach behaviors (per the reciprocal influence hypothesized in the fear avoidance model).

ANS dysregulation has been studied in the context of depression and anxiety disorders. Compared to healthy controls, adolescent girls with emotional disorders, including depression

and anxiety, showed dysregulated ANS activity, as measured by $EtCO_2$, heart rate, heart rate variability (HRV) and respiration rate (RR; Blom et al., 2014). $EtCO_2$, heart rate, and HRV independently predicted group status (i.e., patient versus control) and lower $EtCO_2$ and higher RR were significantly associated with higher symptom severity. Low baseline pCO_2 has also been shown to predict higher anxiety symptom severity and lower quality of life post 12-weeks of psychotherapy and at follow-up in adults (Davies & Craske, 2014). This finding suggests the influence of dysregulated ANS activity on anxiety symptoms and response to psychological treatment, which highlights the importance of considering interactions between psychological factors and ANS functioning and directly targeting ANS dysregulation during psychological treatments. Capnometry-assisted respiratory training (CART) represents a promising intervention to target ANS functioning by way of normalizing CO_2 levels. A study comparing CART to pain-related cognitive restructuring in a sample of adult patients with panic disorder and agoraphobia found comparable improvements in perceived control and reductions in panic-related cognitions and symptoms between treatment conditions (Meuret, Rosenfield, Seidel, Bhaskara, & Hofmann, 2010). However, only CART corrected baseline hypocapnic levels post-treatment (Meuret et al., 2010). Another study using CART to examine whether changes in pCO_2 mediate changes in fear of bodily sensations in a sample of individuals with panic disorder revealed that changes in pCO_2 partially mediated changes in fear of bodily sensations, such that earlier pCO_2 levels predicted later levels of fear of bodily sensations (Meuret, Rosenfield, Hofmann, Suvak, & Roth, 2009). These findings provide support for the use of CART in normalizing ANS function, as well as reducing pain-related cognitive distortions.

The present study incorporated the 4-week CART intervention to target the hypothesized dysregulated ANS functioning in PPCS. Interestingly, a study by Meuret, Hofmann, and

Rosenfield (2010) found that catastrophic appraisal and perceived control moderated treatment response to CART and cognitive skill training in adults with panic disorder and agoraphobia. Overall, reductions in panic symptom severity did not differ between treatments, however, individuals with greater initial levels of catastrophic appraisal showed greater improvement in panic symptoms when receiving CART versus cognitive training, whereas individuals with greater lack of perceived control showed greater improvement in panic symptoms when receiving cognitive training versus CART (Meuret, Hofmann, & Rosenfield, 2010). This finding provides support for the inclusion of both cognitive restructuring and CART in the present treatment manual to account for potential individual differences.

Evidence for Self-Guided CBT

A wealth of research exists supporting the effectiveness of self-guided CBT interventions. A 2010 meta-analysis examining the effectiveness of computerized CBT versus control for adults with anxiety and depressive disorders conducted by Andrews, Cuijpers, Craske, McEvoy, and Titov found that computer-based CBT was superior to control conditions (predominantly waitlist control) and equally effective as traditional face-to-face CBT. Further, benefits of computer-based CBT were maintained at a median of 26-week follow-up (Andrews et al., 2010). A 2012 systematic review conducted by Hedman, Ljótsson and Lindefors examining RCTs comparing internet-based CBT to face-to-face CBT for adults with 25 different clinical disorders found similar results, indicating that internet-based CBT is equally as effective as face-to-face CBT for a given disorder. Effect sizes were large for treatment of depression, anxiety disorders, severe health anxiety, irritable bowel syndrome, female sexual dysfunction, eating disorders, cannabis use disorder and pathological gambling and small to moderate for other clinical conditions (Hedman et al., 2012), suggesting that internet-based CBT may be beneficial

for a wide variety of clinical problems. Additionally, the home-based nature of the interventions and limited therapist time required make internet-based CBT highly cost-effective and more readily accessible (Hedman et al., 2012). Fewer studies exist examining the use of computer - based CBT in adolescents, however, the existing literature suggests similar results as in adults. An RCT comparing an internet-based CBT to face-to-face CBT and a waitlist-control condition for adolescent anxiety found both internet-based and face-to-face CBT resulted in significantly greater improvements in anxiety versus the wait list condition (Spence et al., 2011). Improvements were comparable between active conditions and were maintained or further enhanced at six- and twelve-month follow-ups (Spence et al., 2011). These findings support the use of self-guided CBT interventions for both adults and adolescent samples.

The degree to which therapists are involved in self-guided CBT varies depending on the study but is important to consider as a technique for enhancing self-guided treatment outcomes given research identifying the therapeutic alliance as a strong predictor of treatment outcome (e.g., Krupnick et al., 1996). Newman, Szkodny, Llera, and Przeworski (2011) reviewed the literature on technology-assisted self-help therapies with minimal therapist contact for the treatment of anxiety and depression. They identified four categorical levels of therapist contact: 1) 'self-administered therapy' ("therapist contact for assessment, at most"), 2) 'predominantly self-help' ("therapist contact beyond assessment is for periodic check-ins, teaching clients how to use the self-help tool, and/or for providing the initial therapeutic rationale"), 3) 'minimal-contact therapy' ("active involvement of a therapist, though to a less degree than traditional therapy for this disorder, includes any treatment in which the therapist assists the client in the application of specific therapy techniques and that involves more than 1.5h of a therapist's time"), and 4) 'predominantly therapist-administered treatments' ("clients have regular contact

with a therapist for a typical number of sessions, but the study attempts to determine whether the use of a self-help tool augments the impact of the standard therapy"; Newman et al., 2011). Results suggest that the optimal degree of contact may vary depending on diagnosis and individual differences (Newman et al., 2011). The review found that self-administered and predominantly self-help treatments are most effective for anxiety disorder treatment when clients are motivated. However, when accounting for attrition and compliance, 'minimal-contact therapies' are most effective for many anxiety disorders. Additionally, 'therapist-administered treatments' are the most effective for clinical levels of depression, whereas 'predominantly self-help' interventions are optimal in subthreshold mood disorders. The present study employed a self-guided 'minimal-contact' therapeutic design, which will allow patients to largely guide themselves through treatment while ensuring regular access to a clinician to answer treatment-related questions and provide support. Our novel treatment manual is structured similar to that of a traditional panic disorder treatment (i.e., exposure, cognitive restructuring and CART) due to common underlying mechanisms. Newman and colleagues (2011) identified 'minimal therapist contact' as the optimal contact amount for treatment of panic disorder, which may suggest it is similarly optimal for the treatment of PPCS.

Study Aims and Hypotheses

The present study proposed a biopsychosocial model of PPCS building on the literatures linking ANS dysregulation and the fear avoidance model to PPCS. We tested the efficacy of a six-week home-based CBT intervention specifically targeting ANS dysregulation, avoidance behaviors, and pain-related catastrophic thoughts to reduce PPCS symptoms. Given the increased risk of PPCS in younger ages, the present study examined treatment effects in an adolescent and young adult sample. Borrowing from the CBT evidence bases for depression, anxiety, and bodily

distress syndromes, such as chronic pain, the present study utilized exposure therapy to reduce avoidance behaviors, cognitive restructuring to reduce concussion- and symptom-related catastrophic thinking, and CART to normalize ANS functioning. This intervention represents a novel approach to treating PPCS by combining psychological and physiological strategies to specifically target hypothesized underlying mechanisms rather than PPCS symptoms. A multiple baseline design was used to assess the effect of the intervention on avoidance behaviors, pain catastrophizing, and post-concussion symptoms. Primary hypotheses included the following: 1) daily measures (i.e., levels of avoidance behaviors, pain catastrophizing, and post-concussion symptoms) would be stable across the baseline phase and decrease during the treatment phase, 2) the battery of questionnaires would show improvements from pre- to post-treatment and gains would be maintained at 6-weeks follow-up. Secondary hypotheses included the following: 1) significant improvements in the daily measures and ANS dysregulation (as measured by EtCO2 and pulse rate) over the treatment phase and 2) avoidance, pain catastrophizing, $EtCO_2$ and PR would mediate the effect of treatment on PPCS symptoms.

Methods

Study Design and Setting

Data was collected as part of a multiple baseline single-case design. Data collection occurred between June 2018 and February 2020. The study was approved by the University of California, Los Angeles (UCLA) Institutional Review Board and informed consent and assent (if under the age of 18) were obtained for all participants.

Participants

A total of 9 participants with PPCS enrolled in the study. Participants were recruited from university-affiliated concussion clinics in Los Angeles, CA presenting for a neuropsychological evaluation and treatment consultation. Participants who were diagnosed with PPCS at the clinical evaluation were told about the home-based CBT study as a potential treatment option. Interested participants were screened for eligibility by a clinical research staff member at their visit. After providing consent and assent, participants were randomized to a 2-week (n = 4) or 4-week (n = 5) baseline period prior to beginning the intervention.

Eligibility Criteria

Eligibility criteria included the following: 1) All participants were between the ages of 13 and 25 years-old at study entry; 2) Participants must have sustained a concussion diagnosed by a medical provider within 2- to 16-months of study entry and endorsed persistent post-concussive symptoms using the Post-Concussion Symptom Inventory (PCSI-SR13; Gioia, Janusz, Vaughan, & Sady, 2011-2014); PPCS was confirmed if participants endorsed experiencing symptoms in any of the four symptom domains (i.e., physical, cognitive, emotional, sleep) since sustaining their concussion; and 3) Participants had to demonstrate behavioral avoidance of at least one activity due to the concussion/symptoms at the time of the assessment (determined by a score of ≥1 on the UCLA Return to Activity Avoidance Inventory Avoidance subscale measure). Participants were eligible for the study if they were taking supplements (i.e., riboflavin, magnesium, melatonin) or non-SNRI psychotropic medications (e.g., Amitriptyline, Tricyclics) for headache, so long as the dosage was not at a psychoactive level (i.e., exceeds 50 milligrams). Individuals who were taking non-SNRI psychotropic medications for psychiatric conditions were

required to remain on a stable dose for at least one month prior to starting the study and remain on a stable dose throughout the study. Very little evidence exists supporting the use of pharmacotherapy for PPCS (Hadanny & Efrati, 2016) thus we do not anticipate medication interfering with treatment effects.

Exclusion Criteria

Participants were excluded from the study if they: 1) had any comorbid neurological conditions (i.e., history of stroke, seizure disorder, moderate to severe traumatic brain injury, anoxia) or any severe cardiovascular condition; 2) had a history of psychosis; 3) had current substance abuse or dependence; 4) were currently experiencing severe symptoms of depression; 5) were currently taking or beginning a dose of gabapentin or serotonin-norepinephrine reuptake inhibitors (SNRIs) for headache or psychiatric conditions; and 5) were not fluent in English.

Measures

Beck Anxiety Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988). The BAI is a 21-item questionnaire measuring anxiety severity. The BAI measures symptoms in two factors: somatic symptoms and subjective anxiety and panic symptoms. Respondents use a four-point scale (0 = "Not at all" and 4 = "Severely – I could barely stand it") to rate how much they have been bothered by each symptom over the past one week. Scores range from 0 to 63, where higher scores indicate more severe anxiety. Score interpretations are as follows: mild anxiety: 0-21, moderate anxiety: 22-35, severe anxiety ≥ 36. The BAI has demonstrated high internal consistency ($\alpha = 0.92 – 0.94$) and test-rest reliability over one-week and an average of 11-days ($r = 0.67 – 0.72$), and good convergent and discriminant validity (Beck et al., 1988; Fydrich, Dowdall, & Chambless, 1992). Psychometric properties of the BAI were comparable in a sample

of high school and psychiatric inpatient adolescents, demonstrating good reliability (α = 0.88 – 0.92), test-retest reliability (r = 0.71), and adequate convergent and discriminant validity (Osman et al., 2002).

Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996). The BDI-II is a 21-item questionnaire measuring depression symptom severity over the past two weeks. Items are rated on a zero- to three-point scale with scores ranging from 0 to 63, where higher scores indicate more severe depression. Score interpretations are as follows: minimal depression: 0-13, mild depression: 14-19, moderate depression: 20-28, severe depression: ≥ 29. The BDI-II has demonstrated high internal consistency in outpatient psychiatric adult (α = 0.92; Steer, Ball, Ranieri, & Beck, 1997) and adolescent samples (α = 0.92; Steer, Kumar, Ranieri, & Beck, 1998) and non-clinical young adults (α = 0.90; Osman et al., 1997) and adolescent samples (α = 0.92; Osman, Barrios, Gutierrez, Williams, & Bailey, 2008). It has also demonstrated good test-rest reliability and convergent and discriminant validity (Beck et al., 1996; Sprinkle et al., 2002).

Brief Illness Perception Questionnaire (BIPQ; Broadbent, Petrie, Main, & Weinman, 2006). The BIPQ is a nine-item questionnaire assessing cognitive and emotional representations of illness. Items are rated on a zero- to ten-point scale. Scores range from 0 to 80, where higher scores indicate stronger negative emotional responses to illness and beliefs around the negative impacts of illness. The BIPQ does not specify a clinical cutoff score. The BIPQ has demonstrated good test-retest reliability and concurrent, predictive, and discriminant validity in illness populations ranging from ages 8- to 80-years-old (Broadbent et al., 2006; Broadbent et al., 2015).

Pain Catastrophizing Scale (PCS; Sullivan, Bishop & Pivik, 1995). The PCS is a 13-item questionnaire assessing the degree to which one experiences catastrophic thoughts and feelings

while experiencing pain. Items are rated using a five-point scale from "Not at all" to "Extremely". Scores range from 0 to 52, where higher scores indicate more pain catastrophizing. A score of ≥30 has been identified as a clinically relevant level of pain catastrophizing, corresponding to the 75th percentile of PCS scores among clinical samples of chronic pain patients. Scores of ≥30 are associated with severe functional impairment, including unemployment one-year post injury. The PCS yields a total score and three subscale scores: rumination, magnification and helplessness. The PCS has demonstrated adequate to excellent internal consistency for both the total score ($\alpha = 0.87$) and subscales (rumination $\alpha = 0.87$, magnification $\alpha = 0.66$, and helplessness $\alpha = 0.78$; Sullivan et al., 1995).

Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds III, Monk, Berman, & Kupfer, 1989). The PSQI is a 19-item questionnaire assessing sleep quality and habits over the past one month. Respondents first provide free-response information on their recent sleep habits (e.g., time went to bed, time to fall asleep, etc.) and then answer the remaining questions using a 4-point scale. Items are scored from zero to three, with lower scores reflecting higher sleep quality. The measure yields a sleep quality global score and seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Global scores range from 0 to 21, where higher scores indicate worse sleep quality. The PSQI does not specify a clinical cutoff score. The seven component scores have shown strong internal homogeneity (i.e., each component score measured a separate aspect of the same overall construct; $\alpha = 0.83$; Buysse et al., 1989). The PSQI also has demonstrated good test-retest reliability, known groups validity (i.e., diagnostic sensitivity and specificity discriminating between good and poor sleepers) and convergent and divergent validity (Buysse et al., 1989; Carpenter & Andrykowski, 1998). The PSQI was originally

developed to assess sleep in adults, however, the measure has also demonstrated good convergent and divergent validity and moderate reliability ($\alpha = 0.72$) in adolescents and young adults (de la Vega et al., 2015).

Post-Concussion Symptom Inventory (PCSI-SR13; Gioia, Janusz, Vaughan, & Sady, 2011-2014). The PCSI-SR13 is a 22-item questionnaire assessing symptom severity at two timepoints: 1) prior to injury and 2) current symptoms over the past 24 hours (post-injury). The PCSI has separate self-report forms for children and adolescents ages 5-7 years old, 8-12 years old, and 13-18 years old (i.e., PCSI-SR13), and a parent report form. The questionnaire assesses post-concussive symptoms in four domains: physical/somatic, sleep/fatigue, emotional, and cognitive (Sady, Vaughan, & Gioia, 2014). Respondents rate how much each of the symptoms has been a problem on a zero- to six-point scale (0 = "not a problem" and 6 = "severe problem"). Scores range from 0 to 126 on the total scale, 0 to 48 on the physical symptoms subscale, 0 to 24 on the emotional symptoms subscale, 0 to 36 on the cognitive symptoms subscale, and 0 to 18 on the sleep substance. Higher scores reflect post-concussion symptoms causing more severe problems. The PCSI-SR13 does not specify clinical cutoff scores. The PCSI-SR13 has demonstrated strong internal consistency both for subscale scores (α= 0.79-0.93) and total symptom score ($\alpha = 0.94$), moderate to strong test-rest reliability for subscales (ICC = 0.64-0.76, r = 0.47-0.61) and total score (ICC = 0.79, r = 0.66), and strong convergent validity with a similar acute post-concussive symptom measure ($r = 0.86$, $p < .001$; Sady et al., 2014). The PCSI-SR13 (and younger versions of the PCSI) was originally adapted from the Post-concussion Scale (Lovell & Collins, 1998; Lovell et al., 2006), which measures post-concussive symptoms in adults, to account for developmental differences in vocabulary across younger age ranges (Sady et al., 2014). For consistency purposes, all participants completed the PCSI-SR13 to assess

post-concussive symptoms regardless of age, as participants older than 18-years do not have difficulty accurately completing the PCSI-SR13.

Sheehan Disability Scale (SDS; Sheehan, 1983). The Sheehan Disability Scale is a 3-item questionnaire assessing disability and impairment related to "symptoms" (in this case, participants will consider "symptoms" to mean PPCS symptoms). Participants indicate how much their symptoms have interfered in three domains of life: work/school, social life, and family life/home responsibilities. Items are rated on a zero- to ten-point scale (0 = "not at all" and 10 = "extremely"). Respondents also indicate the number of days in the last week 1) symptoms were so impairing that had to miss school/work or were unable to complete normal daily responsibilities and 2) symptoms felt so impairing productivity was reduced even if they attended work/school. Scores range from 0 (unimpaired) to 30 (highly impaired). The SDS does not specify clinical cutoff scores but notes that scores >5 in any one domain may be indicative of functional impairment. The questionnaire has demonstrated high internal consistency ($\alpha = 0.89$) and good construct validity in a primary care sample (Leon, Olfson, Portera, Farber, & Sheehan, 1997), as well as adequate internal consistency, construct validity, and criterion-related validity in panic disorder (Leon, Shear, Portera, & Klerman, 1992).

UCLA Return to Activity Avoidance Inventory (RAAvI). The RAAvI is a nine-item questionnaire developed by our research team at UCLA as a tool to quickly assess current likelihood of activity avoidance and level of distress when engaging in avoided activities (see Appendix A for the full measure). Modeled off the Fear Hierarchy utilized in exposure therapy, participants first identify the top three activities they have been avoiding since their concussion. They then rate 1) the likelihood of avoiding each of the activities on a five-point scale from "None of the time" to "All of the time" and 2) how emotionally or physically distressed they

would be doing the activity on a five-point scale from “None” to “Extreme”. Avoidance and distress ratings were computed by summing the three responses for each of the domains.

Daily measures. Daily measure questionnaires were collected every day of the baseline and treatment phases as part of the multiple baseline design. The daily measures assessed activity engagement, pain catastrophizing, and post-concussion symptoms in the previous 24 hours. The activity engagement daily measure was developed by our research team at UCLA for the present study and asked participants to rate how engaged they were in the three activities they reported avoiding in the RAAvI using the following scale: 0 = I didn’t do the activity at all, 1 = I engaged the bare minimum to get by, 2 = I was a little engaged, 3 = I was moderately engaged, 4 = I was very engaged, and 5 = I went all in. Scores ranged from 0 to 15 with higher scores reflecting more engagement). The pain catastrophizing daily measure used 5 items from the PCS (Sullivan, Bishop & Pivik, 1995) to reduce patient burden, to assess the degree to which participants experienced catastrophic thoughts while experiencing pain. Scores ranged from 0 to 20 with higher scores indicating more pain catastrophizing. The post-concussion symptoms daily measure assessed 9 common symptoms across the 4 symptom domains: headache, dizziness, tiredness/fatigue, difficulty sleeping, irritability, sadness, nervousness/anxiety, feeling slowed down, and difficulty concentrating. Items were rated using the scale from the PCSI-SR13 (Gioia, Janusz, Vaughan, & Sady, 2011-2014) for ease of comparison across measures. Scores ranged from 0 to 54 for total symptoms, 0 to 12 for physical, cognitive and sleep symptoms, and 0 to 15 for emotional symptoms with higher scores indicating more symptom-related problems. The daily measures were administered on a rotating basis so that each measure was collected once every three days to reduce patient burden.

Capnometry Measurement

Capnometry-Assisted Respiratory Training (CART) utilized The Capnostream^{TM} 35 portable capnometer (Medtronic Inc., Minneapolis, MN, USA) to measure the primary autonomic outcomes of interest, end tidal CO2 (EtCO2; mmHg) and pulse rate (PR; number of heart beats per minute). Respiration rate (RR, number of breaths taken per minute) and oxygen saturation (SpO2, percentage of oxygen bound to hemoglobin) were collected as additional metrics of ANS functioning. Data were sampled at a rate of $f_s = 1$. RR was used to guide CART practices (i.e., participants practiced breathing at specific RRs while maintaining $EtCO_2$ levels in the normal range). A nasal cannula attached to the capnometer measured $EtCO_2$ and RR. A pulse oximeter attached to the capnometer and placed on the participants' non-dominant pointer finger collected PR and SpO_2. On the first day of Module 2 (Feelings) participants were instructed on how to set up the capnometer and were oriented to the audio-guided CART practice. Each CART practice included 2-minutes of rest (baseline phase), 10 minutes of audio-guided breathing (pacing phase), and 5-minutes of practicing breathing at the designated RR and $EtCO_2$ without tones (transition phase). Resting cardiorespiratory values were computed by averaging the values over the 2-minute baseline period. For participants who completed two practices in a day, their baseline values for the two practices were averaged to compute one baseline metric per day. Participants were instructed to complete each CART practice while in a seated upright position and avoid talking. For the baseline phase, participants were asked to breathe normally. Capnometry units were calibrated once prior to the start of the study and no re-calibration took place during data collection in accordance with manufacturer's instructions.

Intervention

As previously mentioned, the present intervention was a six-week home-based cognitive behavioral therapy focusing on reducing avoidance behaviors and catastrophic thinking and normalizing ANS functioning. The treatment structure was as follows: Psychoeducation and treatment rationale, followed by three modules, each focusing on a unique skill. Modules were introduced every two weeks. Participants completed the treatment from home and had check-ins with a research clinician once per week over the phone or Zoom. On day 1 of treatment (Session 1), participants reviewed the psychoeducation and treatment rationale and began Module 1. Session 1 was led by a research clinician over Zoom to ensure understanding of the treatment rationale and exposure psychoeducation, and facilitate treatment buy-in. The treatment rationale and introduction to Module 1 took roughly 90-minutes to complete. The introduction to Module 2 (beginning week 3 of treatment) was also led by a research clinician over Zoom to orient participants to using the capnometer biofeedback device. The introduction to Module 2 took roughly 60-minutes to complete. During the remaining four-weeks of treatment participants touched base with the research clinician once per week for 10-15 minutes to address treatment-related questions and get support. Participants were instructed to continue practicing the skills from previous modules when beginning new modules.

Psychoeducation & Treatment Rationale

During Psychoeducation and treatment rationale participants learned about the CBT mood cycle (i.e., learning how thoughts feelings and behaviors are connected) and how negative thoughts, behaviors and feelings prolong post-concussion recovery. Participants were oriented to the structure of the treatment and identified treatment goals.

Module 1: Exposure

Module 1 (beginning week one) focused on the 'behaviors' component of the mood cycle. Specifically, Module 1 reviewed how avoidance contributes to persistent post-concussion symptoms. Participants learned about the negative consequences of avoidance and were given the rationale for exposure therapy. Participants generated an avoidance fear hierarchy that was used to guide exposure practices. Step-by-step instructions on how to design exposures were included in the manual. Participants designed and engaged in one exposure practice during the introductory session with the research clinician over Zoom. Participants were instructed to continue practicing daily exposure for the remainder of treatment.

Module 2: CART

Module 2 (beginning week three) focused on the 'feelings' component of the mood cycle. Specifically, Module 2 reviewed how the body physically responds to stress. Participants learned about the fight-or-flight response and how chronic fight-or-flight activation can generate physical discomfort that overlaps with post-concussion symptoms. Next, they were provided rationale for targeting breathing to regulate the fight-or-flight response and review the psychoeducation for CART. CART is a four-week respiratory training that focuses on regulating $EtCO_2$ by altering volume of breath and respiration rate (RR; frequency/speed of breath). CART practice involved following a guided audio recording while using the biofeedback device (i.e., capnometer) to monitor $EtCO_2$ levels and RR twice a day. Each week of CART, participants were instructed to practice breathing at a designated RR while trying to maintain a CO_2 level between 37 and 43 mmHg. Practices were led by an audio recording, which included a pacing tone to guide the RR. Each breathing exercise lasted 17 minutes and involved three phrases: 1)

baseline phase (2 minutes; breathing at natural RR and depth), 2) pacing phase (10 minutes; practicing breathing to tones at specific RR while maintaining normal range of CO_2), and 3) transition phase (5 minutes; practicing maintaining RR and CO_2 from 'pacing phase' without the tones). Step-by-step instructions on how to set up the capnometer and download the data were included in the manual. Participants completed one CART practice during the introductory session with the research clinician over Zoom. Participants were instructed to complete two CART practices per day for the remainder of treatment.

Module 3: Cognitive Restructuring

Module 3 (beginning week 5) focused on the 'thoughts' component of the mood cycle. Specifically, Module 3 reviewed how catastrophizing (i.e., overestimating the threat of physical discomfort and underestimating one's ability to cope with physical discomfort) perpetuates post-concussion symptoms. Participants were taught how to identify their catastrophic thoughts and use evidence to challenge catastrophic thoughts and replace them with more balanced and accurate thoughts. Participants were introduced to two worksheets used to challenge catastrophic thoughts. The first worksheet challenged thoughts that overestimate the likelihood of negative events occurring, and the second worksheet challenged thoughts that overestimate how extreme a negative situation will be and underestimate the participant's ability to cope with the outcome. Participants were instructed to complete one thought-challenging worksheet per day for the remainder of treatment.

Multiple Baseline Design

A multiple baseline design was used to assess the effects of the CBT intervention on post-concussion symptoms (main outcome) and level of avoidance and degree of pain-related

catastrophic thinking (treatment targets). Participants were randomized to one of two baseline durations (two or four weeks) prior to beginning treatment. Throughout baseline and treatment phases participants provided daily ratings of avoidance, pain catastrophizing, and post-concussion symptoms through online questionnaires to assess stability of the measures during baseline and changes in the measures following introduction of the intervention. The randomization to baseline lengths allows for drawing causal inferences about the effect of treatment on daily measures (Kazdin, 2003; see description of multiple baseline designs in the Single Case Designs section of the Introduction for additional details).

Procedure

Nine participants with PPCS were recruited from outpatient concussion clinics. A comprehensive history was collected for all patients presenting at the BrainSPORT Clinic for a clinical evaluation. PPCS diagnosis was confirmed during this clinical visit by 1) confirming history of diagnosed concussion (i.e., occurrence of biomechanical force directly before onset of post-concussive symptoms); 2) temporal onset of symptoms within 24 hours of injury; 3) continuous post-concussive symptoms for 2 – 16 months post-injury. The clinicians running the clinic evaluations at BrainSPORT were familiar with the research eligibility and exclusion criteria and determined from data collected during the evaluation whether a patient was eligible for the study. Participants with confirmed PPCS and who met eligibility were told about the home-based CBT study as a potential treatment option. Interested and eligible participants were then consented and randomized into the two- or four-week baseline. In multiple baseline designs the numerous baseline lengths typically vary up to the length of the intervention, however, in the present study, participants were experiencing distressing functional impairment that necessitated the initiation of treatment as soon as possible. Thus, only two baseline lengths up to four-weeks

were utilized. Randomization was achieved using Sealed Envelope, an online block randomization program for clinical trials (Sealed Envelope Ltd., 2021). Randomization used block sizes of 4 and was stratified by sex.

All participants were assigned a study ID to deidentify their data. Participants were oriented to the online surveys used to collect daily measures, delivered through Qualtrics. Participants began completing daily surveys on the first day of the baseline phase (day after they consented to participate) and continued completing daily measures through the last day of the treatment phase. A survey link was sent to participants via email at 3pm each day with reminders sent at 6pm. The daily measures took no more than two-minutes to complete. Participants completed a battery of questionnaires, consisting of the BAI, BDI-II, the Brief IPQ, PCS, PCSI-SR13, PSQI, the SDS, and the UCLA RAAvI, during the baseline phase prior to beginning the intervention as their pre-treatment assessment.

Immediately following the baseline phase, participants began the CBT intervention. Participants accessed the treatment manual in PDF form online through UCLA Box. They were emailed detailed instructions on how to set up a Box account and access their manual. Participants scheduled a 90-minute Zoom session with their research clinician on the first day of the intervention to review the treatment rationale and Module 1. Participants were instructed to complete daily treatment practices on their own throughout treatment. Participants scheduled a 60-minute Zoom session with the research clinician during week 3 to review Module 2 and orient participants to using the capnometer. Participants were either provided a capnometer to take home with them from the consenting visit or were mailed a capnometer to their home prior to beginning Module 2. Participants were instructed to upload their data from the capnometer to the Box once per week.

Participants completed the same battery of questionnaires collected at pre-treatment after completing the intervention (i.e., BAI, BDI-II, the Brief IPQ, PCS, PCSI-SR13, PSQI, the SDS, and the UCLA RAAvI). Participants also completed a subset of the battery of questionnaires (to reduce participant burden) assessing the main outcome variables (i.e., PCS, PCSI-SR13, and the UCLA RAAvI) again six-weeks post-treatment to assess whether treatment-related improvements were maintained. See Figure 1 for a visual depiction of the study flow.

Statistical Analysis Plan

Primary Hypotheses

Daily Measures

To examine the effects of the intervention versus baseline phase on the daily measures, multiple baseline data were analyzed using 1) visual inspection of the daily measures trajectories during the baseline and treatment phases, and 2) complementary non-parametric randomization tests for multiple baseline data. Graphical representations of the daily measures were visually inspected for a) stability of the daily measures during the baseline phase, b) magnitude of change in the daily measures at the introduction of the treatment, and c) slope of the daily measures during the treatment phase. Follow-up statistical randomization tests were then conducted to determine whether observed differences were significant.

Randomization tests rely on some aspect of the design being randomized (Bulté & Onghena, 2009). Statistical significance was determined by calculating the observed test statistic (i.e., mean difference) and comparing it to a random sample of test statistics generated by 1000 Monte Carlo randomization simulations (e.g., Ferron & Onghena, 1996; Ferron & Sentovich, 2002; Bulté & Onghena, 2009). The randomization test's p-value is equal to the proportion of test statistics out of the distribution of test statistics that equal or exceed the observed test

statistic. Results are considered significant if the p-value is less than or equal to the predetermined alpha threshold (i.e., $p < .05$; e.g., Bulté & Onghena, 2009). The standardized mean difference was also calculated as a measure of effect size (i.e., Cohen's d statistic). Randomization tests were conducted using The Shiny Single-Case Design Analysis (v2.8) web application programmed in R-studio created by Tamal Kumar De, Bart Michiels, Johan W.S. Vlaeyen and Patrick Onghena (Bulté & Onghena, 2013; 2016).

Questionnaires

A battery of questionnaires was administered to participants before treatment, after treatment and at 6-weeks post-treatment. In keeping with a multiple baseline design, questionnaires were examined at the individual level by calculating the percent change in questionnaire scores between pre-treatment, post-treatment and 6-weeks post-treatment for each participant. Follow-up group level analyses were conducted to examine changes in the sample. Paired-samples t-tests were used to measure differences at pre-treatment, post-treatment and 6-weeks post-treatment. Paired samples t-tests were run using SPSS Statistics 27.

Secondary Hypotheses

Secondary hypotheses tested 1) how the daily measures and measures of ANS functioning (i.e., EtCO2 and PR) changed during the treatment phase and 2) whether significant changes in the daily measures and ANS variables mediated the effect of treatment on post-concussion symptoms. Statistical analyses used multilevel mixed effects models to examine changes in the daily measures and ANS measures over the course of the treatment phase. Repeated measures were nested within individuals. Mediation analyses tested three equations (the c path, the a path, and the b path and c prime) to compute the direct and indirect effects of the model. The significance of the indirect effect was tested using bootstrapping procedures.

Unstandardized indirect effects were computed for each 1,000 bootstrapped samples and the 95% confidence interval was computed by determining the indirect effects at the 2.5th and 97.5th percentiles. Mixed effects models and mediation analyses were run using Stata/IC 16.1.

Results

A total of 9 participants with PPCS were recruited from the UCLA outpatient concussion clinic and surrounding community clinics. Demographics for the sample are presented in Table 1. As part of the multiple baseline design participants were randomized to a 2-week (n = 4) or 4-week (n = 5) baseline phase prior to beginning treatment and assessed daily on the following measures: activity engagement, pain catastrophizing, and post-concussion symptoms. A battery of questionnaires, including the UCLA RAAvI, PCS, PCSI-13R, BAI, BDI-II, BIPQ, SDS and PSQI, were collected prior to beginning the treatment and at post-treatment, and a subset of the questionnaires assessing the primary outcome variables were collected at 6-weeks post-treatment (i.e., UCLA RAAvI, PCS, and PCSI-13R). See Tables 2 – 4 for descriptives and correlation coefficients for the questionnaires at pre-treatment, post-treatment and 6-weeks follow-up. Lastly, measures of $EtCO_2$ and PR were collected during the last four weeks of the treatment phase as part of CART to assess ANS functioning.

Primary Hypotheses

Daily Measures

Visual Inspection

Visual inspection was conducted for each participant for each of the daily measures (see 'Participants – Completers' and 'Participants – Lost to Follow-up' sections below for individual visual inspection results and figures of the daily measures). In large, participants did not

demonstrate stabilization of daily measures during the baseline phase, which limited ability to visually detect immediate changes at the start of the treatment phase and differences in slopes between phases. Overall, visual inspection revealed 1) higher scores on average of activity engagement during the treatment vs. baseline phase, 2) lower scores on average of pain catastrophizing during the treatment vs. baseline phase, and 3) lower scores on average of post-concussion symptoms (total, physical, emotion, cognitive, and sleep) during the treatment vs. baseline phase.

Randomization Tests

As recommended by Kazdin (2003), participants were included in multiple baseline analyses if they had at least 4 daily measure observations in both the baseline and treatment phases. Nine participants were included in the randomization analyses of activity engagement and pain catastrophizing; eight participants were included in the randomization analysis of post-concussion symptoms (total and subscales). One participant was excluded from analyses of post-concussion symptoms for having less than 4 observations during the baseline phase due to inconsistent responding.

Randomization tests for multiple baseline designs were conducted for each of the daily measures. Results of the randomization tests revealed non-significant differences between baseline and treatment phases for activity engagement (mean difference {B-A} = 1.80, p = 0.26, Cohen's d = 1.52), pain catastrophizing (mean difference {A-B} = 2.66, p = 0.45, Cohen's d = -1.82), and post-concussion symptoms total (mean difference {A-B} = 5.72, p = 0.13, Cohen's d = -0.98). Randomization tests of post-concussion symptom sub-categories revealed significant reductions in post-concussion sleep symptoms from the baseline to treatment phase (mean difference {A-B} = 1.17, p = 0.02, Cohen's d = -0.59) and trend-level reductions in post-

concussion physical symptoms (mean difference {A-B} = 1.34, p = 0.07, Cohen's d = -0.62). Non-significant differences between baseline and treatment phases were found for post-concussion emotional symptoms (mean difference {A-B} = 1.40, p = 0.57, Cohen's d = -0.59) and cognitive symptoms (mean difference {A-B} = 1.93, p = 0.28, Cohen's d = -1.08).

Questionnaires

Paired Samples T-tests

Six participants completed the battery of questionnaires at pre- and post-treatment and were included in analyses comparing pre- and post-treatment scores. Of those who completed the treatment, four participants completed a subset of questionnaires at 6-weeks follow-up and were included in analyses examining changes in scores from post-treatment to 6-weeks follow-up. Paired samples t-tests revealed significant decreases from pre- to post-treatment in the RAAvI Avoidance subscale ($t(5) = 3.87$, $p = 0.01$), RAAvI Distress subscale ($t(5) = 2.61$, $p = 0.048$), Pain Catastrophizing Scale ($t(5) = 2.69$, $p = 0.04$), and the Brief Illness Perception Questionnaire ($t(5) = 3.27$, $p = 0.02$). There were no significant differences in scores between post-treatment and 6-weeks post-treatment. See Tables 5 and 6 for full results of the paired samples t-tests.

Participants - Completers

Participant 3

Participant 3 (P3) was a 16-year-old female. P3 had a history of one concussion. P3's primary areas of avoidance following her concussion included physical exercise, school (attendance and assignments), and socializing. P3 was randomized to the 2-week baseline condition. She completed daily measures, CART practice, and pre- and post-treatment

questionnaires. P3 did not complete 6-week follow-up questionnaires due to lack of responsiveness.

Daily Measures: P3 was inconsistent with her daily measures responses and therefore had a decent amount of missing data. Her scores were somewhat stable during the baseline phase for activity engagement and pain catastrophizing but did not demonstrate stability in post-concussion symptom scores (i.e., demonstrated a moderate decrease between the first two baseline measurements for total, which appears to be driven by decreases in physical and cognitive symptoms). Her pain catastrophizing and post-concussion symptom scores demonstrated downward trends during the treatment phase, with pain catastrophizing showing an immediate reduction at the start of the intervention. Activity engagement initially showed an upward trend during the treatment phase, but the final daily measure data point reflected a decrease in activity engagement, thus minimizing the overall slope of change across the treatment phase. P3's daily measure graphs (i.e., activity engagement, pain catastrophizing, post-concussion symptoms total, and post-concussion symptoms by symptom category) are presented in Figure 2a-d. For the figures depicting post-concussion symptoms by symptom category, only symptom domains that reached statistical significance in the randomization tests (i.e., physical and sleep) are presented for each participant, for ease of visualization.

Questionnaires: P3 demonstrated reductions in scores from pre-treatment to post-treatment in the RAAvI Avoidance and Distress scales, PCS, PCSI total, physical and cognitive scales, BAI, BIPQ, and SDS, suggesting improvements in each of these domains. Her scores on the PCSI emotional scale and BDI-II showed no changes post-treatment. Her score on the PSQI and PCSI sleep scale showed increases following treatment, suggesting worsening sleep quality

post-treatment. See Table 7 for pre- to post-treatment percent change scores for each questionnaire.

CART: P3 completed 13 CART practices across nine days during weeks 3-6 of the treatment phase. P3's resting $EtCO_2$ levels were in the normal range at her first practice. Over the course of treatment her resting $EtCO_2$, PR, RR and SpO_2 values fluctuated but did not trend in any particular direction, suggesting CART did not alter resting ANS functioning. P3's CART graphs are presented in Figure 3a-d.

Participant 6

Participant 6 (P6) was a 14-year-old female. P6 had a history of four concussions. P6's primary arears of avoidance following her concussion included physical exercise, school (attendance and assignments), and socializing. P6 was randomized to the 2-week baseline condition. She completed daily measures, CART practice, and pre- and post-treatment and 6-week follow-up questionnaires.

Daily Measures: P6 demonstrated slight stability during the baseline phase for activity engagement but did not show baseline stability for pain catastrophizing (i.e., downward trend) and post-concussion symptoms (i.e., large decrease between first two measurements followed by stability for remainder of baseline, largely driven by a decrease in post-concussion emotion symptoms). Activity engagement demonstrated an increase at the intervention start and upward trend over the course of treatment. Pain catastrophizing did not demonstrate a marked difference at treatment start or a slope over the treatment phase. Post-concussion symptoms showed a slight decrease at the treatment start but did not show much change over the treatment phase. P6's daily measure graphs are presented in Figure 4a-d.

Questionnaires: P6 demonstrated reductions from pre- to post-treatment in all questionnaires, suggesting improvements in all domains. At 6-weeks follow-up P6's scores on the RAAvI Avoidance and Distress scales and PCSI emotional subscale remained unchanged from post-treatment, suggesting that improvements were maintained. The PCS showed additional reductions from post-treatment to 6-weeks follow-up. Scores on the PCSI total, physical, cognitive and sleep subscales demonstrated increases from post-treatment to 6-weeks follow-up, however, follow-up scores were still lower than pre-treatment scores, suggesting overall improvements from pre-treatment to follow-up. See Table 7 and 8 for pre-, post-treatment and 6-week follow-up percent change scores for each questionnaire.

CART: P6 completed 46 CART practices across 24 days during weeks 3-6 of the treatment phase. P6's resting $EtCO_2$ levels were in the normal range at her first practice and throughout treatment. Over the course of CART her resting $EtCO_2$, RR and SpO_2 values fluctuated but did not trend in any particular direction, suggesting CART did not alter resting $EtCO_2$, RR and SpO_2. P6's resting PR appeared to demonstrate a slight upward trend over the treatment phase. P6's CART graphs are presented in Figure 5a-d.

Participant 7

Participant 7 (P7) was a 17-year-old female. P7 had a history of one concussion. P7's primary areas of avoidance following her concussion included physical exercise and school (attendance and assignments). P7 was randomized to the 4-week baseline condition. She completed daily measures, CART practice, and pre- and post-treatment and 6-week follow-up questionnaires.

Daily Measures: P7 did not demonstrate stability during the baseline phase for activity engagement, pain catastrophizing or post-concussion symptoms. Activity engagement showed a

mild increase at the intervention start but increases were inconsistent. Both pain catastrophizing and post-concussion symptoms showed a decrease at the start of the treatment. Post-concussion symptoms continued to fluctuate over the treatment phase. Pain catastrophizing showed a downward trend during the intervention. P7's daily measures graphs are presented in Figure 6a-d.

Questionnaires: P7 demonstrated reductions from pre- to post-treatment on the RAAvI Avoidance scale, PCS, PCSI total and subscales, BAI, BDI-II, BIPQ and SDS and additional reductions in the RAAvI avoidance scale, PCS and PCSI at 6-weeks follow-up, suggesting improvements in these domains during treatment that continued 6-weeks post-treatment. Her scores increased on the RAAvI Distress scale and PSQI from pre-treatment to post-treatment. However, the RAAvI was collected again at 6-weeks follow-up and her score on the distress scale was lower than both pre- and post-treatment scores, suggesting overall improvements from pre-treatment to follow-up. See Table 7 and 8 for pre-, post-treatment and 6-week follow-up percent change scores for each questionnaire.

CART: P7 completed seven CART practices across six days during weeks 3-6 of the treatment phase. P7's resting $EtCO_2$ levels were below the normal range at her first practice. Resting $EtCO_2$ and PR values showed a slight upward trend over treatment. Resting RR and SpO_2 values fluctuated but did not trend in any particular direction, suggesting CART did not alter resting RR and SpO_2. P7's CART graphs are presented in Figure 7a-d.

Participant 8

Participant 8 (P8) was a 16-year-old male. P8 had a history of one concussion. P8's primary areas of avoidance following his concussion included physical exercise and school

assignments. P8 was randomized to the 4-week baseline condition. He completed daily measures, CART practice, and pre- and post-treatment and 6-week follow-up questionnaires.

Daily Measures: P8 did not demonstrate baseline stability for activity engagement, pain catastrophizing or post-concussion symptoms. His responses were variable in all three measures throughout the treatment phase and did not demonstrate a clear trend over time. Interestingly, P8 experienced a large spike in scores of all three measures towards the end of the treatment phase. A possible explanation is that P8 experienced an increase in post-concussion symptoms while engaging in activities which may have led to pain catastrophizing. An alternate explanation is that an increase in pain catastrophizing while engaging in activities elicited an increase in symptoms. P8's daily measures graphs are presented in Figure 8a-d.

Questionnaires: P8 demonstrated reductions from pre- to post-treatment on the RAAvI Avoidance and Distress scales, PCS, PCSI total and subscales, BDI-II and BIPQ. His scores on the BAI, SDS and PSQI showed mild increases from pre- to post-treatment. At 6-weeks follow-up his score on the PCSI sleep subscale remained unchanged from post-treatment, whereas his scores on the RAAvI Avoidance and Distress scales, PCS and PCSI cognitive subscale showed continued reductions from post-treatment. Scores on the PCSI total and physical and emotional subscales increased from post-treatment to 6-weeks follow-up, however, the scores at follow-up remained substantially lower than pre-treatment, suggesting overall improvements from pre-treatment to follow-up. See Table 7 and 8 for pre-, post-treatment and 6-week follow-up percent change scores for each questionnaire.

CART: P8 completed 17 CART practices across 16 days during weeks 3-6 of the treatment phase. P8's resting $EtCO_2$ levels were below the normal range at his first practice and demonstrated an upward trend over the course of treatment, rising to the lower limit of the

normal range. Resting RR, PR and SpO_2 values fluctuated over the course of treatment but did not trend in any particular direction, suggesting CART did not alter resting PR, RR and SpO_2. P8's CART graphs are presented in Figure 9a-d.

Participant 9

Participant 9 (P9) was a 15-year-old female. P9 had a history of one concussion. P9's primary areas of avoidance following her concussion included physical exercise and school (attendance and assignments). P9 was randomized to the 4-week baseline condition. She completed daily measures, CART practice, and pre- and post-treatment and 6-week follow-up questionnaires (P9 only has responses for the RAAvI at follow-up due to discontinuing the survey early).

Daily Measures: P9 did not demonstrate baseline stability for activity engagement or post-concussion symptoms. Pain catastrophizing scores were slightly more stable during the baseline phase but indicated a slight downward trend. Post-concussion symptoms showed a large decrease near the start of the treatment phase, following a spike at the first measurement of the treatment phase, largely driven by post-concussion emotional symptoms. Activity engagement scores showed variability throughout the treatment phase. Pain catastrophizing and post-concussion symptoms were more stable during the treatment phase, with an increase in scores at the end of treatment. Again, the increase in post-concussion symptoms appeared to be driven by a spike in post-concussion emotional symptoms. P9's daily measures graphs are presented in Figure 10a-d.

Questionnaires: P9 demonstrated reductions from pre- to post-treatment on the RAAvI Avoidance and Distress scales, PCSI emotional and cognitive and subscales, BAI, BDI-II, BIPQ, SDS and PSQI, suggesting improvements in these domains. Her scores on the PCS, PCSI total

and physical subscales showed mild increases from pre- to post-treatment (PCSI total increase was driven by the increase in physical symptoms). The PCSI sleep subscale showed no changes. At 6-weeks follow-up her scores on the RAAvI Avoidance and Distress scales showed additional reductions from post-treatment. See Table 7 and 8 for pre-, post-treatment and 6-week follow-up percent change scores for each questionnaire.

CART: P9 completed 16 CART practices across 15 days during weeks 3-6 of the treatment phase. P9's resting $EtCO_2$ levels were below the normal range at her first practice. Her resting $EtCO_2$, RR, PR and SpO_2 values demonstrated slight fluctuations over the course of treatment but generally remained stable, suggesting that CART did not alter resting ANS functioning. P9's CART graphs are presented in Figure 11a-d.

Participants – Lost to Follow-up

Participant 1

Participant 1 (P1) was a 16-year-old female. P1 had a history of one concussion. P1's primary areas of avoidance following her concussion included physical exercise and school (attendance and assignments). P1 was randomized to the 4-week baseline condition. She completed daily measures, CART practice, and pre-treatment questionnaires. P1 discontinued the treatment at week 5 due to clinically indicated medication changes that were inconsistent with the present study's inclusion criteria. P1 did not complete post-treatment or follow-up questionnaires.

Daily Measures: P1 did not demonstrate baseline stability for activity engagement, pain catastrophizing, or post-concussion symptoms. Her scores on activity engagement increased at the start of treatment but then fluctuated over the course of the treatment phase between no engagement and high levels of engagement. Pain catastrophizing scores showed a decrease at the

start of treatment, followed by an increase, and then remained stable at a lower score for the remainder of treatment. Scores on post-concussion symptoms did not demonstrate an immediate change at treatment start or any clear trend during the treatment phase, which was largely driven by high scores in post-concussion emotional and cognitive symptoms. Post-concussion physical symptoms showed a downward trend during the treatment phase. P1's daily measures graphs are presented in Figure 12a-d.

CART: P1 completed 17 CART practices across 10 days during weeks 3-5 of the treatment phase before discontinuing. P1's resting $EtCO_2$ levels were below the normal range at her first practice. Her resting $EtCO_2$ and PR values demonstrated sharp increases and decreases over the course of treatment with no clear trend over time, suggesting CART practice did not alter resting $EtCO_2$ and PR. Resting SpO_2 also showed fluctuations over treatment with no apparent trend over time. Resting RR demonstrated a slight upward trend over time. P1's CART graphs are presented in Figure 13a-d.

Participant 2

Participant 2 (P2) was a 13-year-old female. P2 had a history of three concussions. P2's primary areas of avoidance following her concussion included physical activity, school (attendance and assignments) and socializing. P2 was randomized to the 4-week baseline condition. She completed daily measures and pre-treatment questionnaires. P2 discontinued the treatment at week 4 of the treatment phase due to lack of interest/engagement. P2 does not have post-treatment and 6-week follow-up questionnaires or CART practice due to discontinuation/lack of engagement. P2 continued completing the daily measures during the last two weeks of the study even after disengaging from the intervention.

Daily Measures: P2's scores on activity engagement were somewhat stable during the baseline phase, whereas her scores on pain catastrophizing and post-concussion symptoms did not demonstrate stability. Activity engagement showed an upward trend during the first few measurements of the treatment phase and more variability towards the end of treatment. Scores on pain catastrophizing and post-concussion symptoms did not demonstrate immediate treatment effects or clear trends over treatment. P2's daily measures graphs are presented in Figure 14a-d.

Participant 4

Participant 4 (P4) was a 21-year-old female. P4 had a history of two concussions. P4's primary areas of avoidance following her concussion included school (attendance and assignments) and physical exercise. P4 was randomized to the 2-week baseline condition. She discontinued the study at week 3 of the treatment phase due to moving and time constraints. P4 completed daily measures and pre-treatment questionnaires. She also completed the post-treatment battery of questionnaires upon treatment discontinuation and her results are included in individual and group-level analyses. P4 does not have 6-week follow-up questionnaires or CART data. At discontinuation, P4 had increased engagement in physical exercise and was engaged in daily practice for her sport.

Daily Measures: P4's scores on activity engagement did not quite reach baseline stability, demonstrating a mild upward trend during the baseline phase. Her scores on pain catastrophizing and post-concussion symptoms did not demonstrate baseline stability. Activity engagement scores decreased initially during the first few days of the treatment and then increased to P4's highest engagement score prior to discontinuation. Pain catastrophizing and post-concussion symptoms increased initially at the start of treatment and then reduced prior to discontinuation. P4's daily measures graphs are presented in Figure 15a-d.

Questionnaires: P4 demonstrated reductions in her pre- to post-treatment scores on the RAAvI Avoidance and Distress scales, PCS, BAI, BIPQ and SDS, suggesting improvements in these domains. Her scores on the PCSI physical and sleep subscales showed no changes. Scores on the PCSI total and emotional and cognitive subscales showed substantial increases at post-treatment compared to pre-treatment (PCSI total increase was driven by the increases in these subscales). The BDI-II and PSQI also demonstrated increases at post-treatment. See Table 7 for pre- and post-treatment percent change scores for each questionnaire.

Participant 5

Participant 5 (P5) was a 19-year-old male. P5 had a history of three concussions. P5's primary areas of avoidance following his concussion included physical exercise and socializing in large crowds. P5 was randomized to the 2-week baseline condition. He discontinued the study at week 3 of the treatment phase due to improvements in symptoms, reductions in behavioral avoidance, and fully returning to sports. P5 completed daily measures and pre-treatment questionnaires. He does not have post-treatment and 6-week follow-up questionnaires or CART data.

Daily Measures: P5's scores on activity engagement were somewhat stable during the baseline phase. Pain catastrophizing and post-concussion symptoms did not demonstrate baseline stability. His scores showed an upward trend in activity engagement and downward trend in pain catastrophizing and post-concussion symptoms over the treatment phase. P5 reported zero pain catastrophizing and post-concussion symptoms for his final 6 measurement responses (weeks 2-3 of treatment) before discontinuing. P5's daily measures graphs are presented in Figure 16a-d.

Secondary Hypotheses

Effect of treatment time on daily measures

Nine participants were included in the multilevel mixed effects analyses examining the change in the daily measures over the course of treatment. Results revealed a significant negative association between treatment time and pain catastrophizing (b = -0.12, SE = 0.05, z = -2.66, p = 0.008, 95% CI = -0.22 to -0.03; $X^2(1) = 7.09$, p = 0.007), such that pain catastrophizing scores decreased 0.12 units for every one-point increase in time (see Figure 17). There was also a significant negative association between treatment time and post-concussion physical symptoms (b = -0.08, SE = 0.04, z = -2.05, p = 0.04, 95% CI = -0.16 to -0.004; $X^2(1) = 4.19$, p = 0.04), such that physical symptom scores decreased 0.08 units for every one-point increase in time (see Figure 18). No associations were observed between treatment time and activity engagement (b = 0.07, SE = 0.08, z = 0.85, p = 0.40, 95% CI = -0.09 to 0.23; $X^2(1) = 0.72$, p = 0.40), post-concussion symptoms total score (b = -0.18, SE = 0.16, z = -1.13, p = 0.26, 95% CI = -0.49 to 0.13; $X^2(1) = 1.28$, p = 0.26), as well as the other post-concussion symptom subset scores: emotional symptoms (b = -0.03, SE = 0.08, z = -0.46, p = 0.65, 95% CI = -0.19 to 0.12; $X^2(1) = 0.21$, p = 0.65), cognitive symptoms (b = -0.07, SE = 0.06, z = -1.30, p = 0.19, 95% CI = -0.18 to 0.04; $X^2(1) = 1.69$, p = 0.19), and sleep symptoms (b = 0.03, SE = 0.05, z = 0.61, p = 0.54, 95% CI = -0.06 to 0.12; $X^2(1) = 0.37$, p = 0.54).

Effect of treatment time on ANS functioning

Six participants engaged in CART during treatment and were included in the multilevel mixed effects analyses examining the effect of CART on $EtCO_2$ and PR. Results revealed that CART time was not significantly associated with $EtCO_2$ (b = 0.05, SE = 0.04, z = 1.34, p = 0.18, 95% CI = -0.02 to 0.12; $X^2(1) = 1.78$, p = 0.18) or PR (b = 0.12, SE = 0.12, z = 1.03, p = 0.30, 95% CI = -0.11 to 0.35; $X^2(1) = 1.06$, p = 0.30).

Mediators of treatment

A mediation analysis was run to test whether pain catastrophizing mediated the effect of treatment on post-concussion physical symptoms. Three equations were run to test the c path (physical symptoms regressed on treatment), the a path (pain catastrophizing regressed on treatment) and the b path and c prime (physical symptoms regressed on pain catastrophizing and treatment time; see Figure 19). The c path demonstrated a significant negative association between treatment time and physical symptoms (b = -0.08, SE = 0.04, z = -2.05, p = 0.04, 95% CI = -0.17 to -0.004; $X^2(1) = 4.21$, p = 0.04). The a path demonstrated a significant negative association between treatment and pain catastrophizing (b = -0.13, SE = 0.05, z = -2.64, p = 0.008, 95% CI = -0.22 to -0.03; $X^2(1) = 6.98$, p = 0.008). The equation testing the b path and c prime demonstrated a significant positive association between pain catastrophizing and physical symptoms (b = 0.25, SE = 0.08, z = 3.22, p = 0.001, 95% CI = 0.09 to 0.40), such that as physical symptoms increased 0.25 units for every one-point increase in pain catastrophizing, whereas treatment was no longer a significant predictor of physical symptoms with pain catastrophizing in the model (b = -0.04, SE = 0.04, z = -1.17, p = 0.24, 95% CI = -0.12 to -0.03; $X^2(2) = 14.23$, $p < 0.001$). The standardized indirect effect was (-0.13)(0.25) = -0.03. The significance of this indirect effect was tested using bootstrapping procedures. The bootstrapped unstandardized indirect effect was not significant (b = -0.03, Bootstrap SE = 0.02, z = -1.61, p = 0.11, 95% CI = -0.07 to -0.01), suggesting that mediation did not meet statistical significance.

Discussion

The present study examined the efficacy of a six-week home-based cognitive behavior therapy (CBT) and capnometry-assisted respiratory training (CART) for persistent post-concussion symptoms (PPCS). The intervention included three therapeutic techniques (i.e.,

exposure, CART and cognitive restructuring) to target three factors hypothesized to underlie PPCS: a) avoidance, b) autonomic dysregulation, as measured by resting $EtCO_2$ and PR, and c) pain catastrophizing. A multiple baseline design in which participants were randomized to a two- or four-week baseline was used to examine the effects of treatment on the three daily measures: post-concussion symptoms, activity engagement and pain catastrophizing. Participants also completed a battery of questionnaires assessing post-concussion symptoms, avoidance and pain catastrophizing, as well as mood and anxiety, sleep quality, injury-related cognitions and functioning before treatment, after treatment and at 6-weeks follow-up. We predicted that the daily measures would remain stable during the baseline phase, demonstrate improvements at the introduction of the intervention and show significant mean differences between the baseline and treatment phases. We also hypothesized that the battery of questionnaires would show improvements from pre- to post-treatment and gains would be maintained at 6-weeks follow-up. Lastly, we predicted that improvements in the activity engagement and pain catastrophizing daily measures and ANS dysregulation (as measured by $EtCO_2$ and PR) would mediate the effect of treatment on post-concussion symptoms.

The results of the multiple baseline visual inspection and randomization tests are promising, suggesting changes in the daily measures during the treatment phase with moderate to large effect sizes. Although the data largely did not demonstrate stability during the baseline or immediate changes at the start of the intervention, visual inspection revealed that daily measure scores were higher on average for activity engagement in the treatment phase than the baseline phase, and lower on average for pain catastrophizing and post-concussion symptoms (total, sleep, physical, cognitive and emotional) in the treatment phase than the baseline phase. Follow-up randomization tests examining mean differences reached significance for post-concussion

sleep symptoms and yielded trend-level effects for post-concussion physical symptoms. Although randomization tests did not reach significance for activity engagement, effect sizes for pain catastrophizing, and post-concussion total and cognitive symptoms were large, suggesting an effect of the intervention. Post-concussion emotional symptoms demonstrated mean differences with a moderate effect size, however, results also did not reach significance. Without reaching statistical significance we cannot rule out the possibility that changes in the daily measures observed during the treatment phase are due to an independent confounding factor rather than the intervention, thus these results must be interpreted with caution.

A few explanations can be offered for why the randomization tests did not meet statistical significance. The power of randomization tests depends on several factors including effect size, number of possible randomization assignments and missing data. Although effect sizes were large and did not hinder power, numerous participants were inconsistent with their daily measure responses, resulting in substantial missing data. In particular P3, P4, and P5 demonstrated the most missing data. P3 was inconsistent with responding, which may reflect reduced engagement in treatment. However, P3's daily measures demonstrated noticeable mean differences in activity engagement, pain catastrophizing, and post-concussion total symptom scores from baseline to treatment and scores trended in the expected direction during treatment, suggesting P3 was engaging in the intervention. P4 was engaged in the study during the baseline phase and first two weeks of the treatment phase, however, midway through the treatment she moved and discontinued from the study due to time constraints. As such, her daily measures are missing data for the second half of the treatment phase. P5 is also missing daily measures data in the second half of the intervention. P5 was engaged in the treatment and demonstrated rapid improvements, including reductions in pain catastrophizing, a nearly 10-point reduction in post-concussion

symptoms at the start of the intervention phase, and an upward trend in activity engagement during the treatment phase. P5 discontinued the study halfway through the intervention due to his improvements and fully returning to his sport.

The present study only had two randomization conditions, which also impacted statistical power by reducing the total number of possible randomization assignments, thus limiting the number of randomization comparisons conducted. Further, as detected in the visual inspection, the daily measures did not demonstrate stability during the baseline phase, which makes it harder to detect changes at the start of the intervention and prevents us from being able to rule out the possibility that changes in scores are due to an independent confounding factor rather than the intervention. The immediacy or delay of the treatment effects also influence randomization tests. Interventions that demonstrate immediate effects may be more resilient to missing data and fewer randomization assignments due to stark changes at the introduction of treatment. For interventions with delayed effects, changes may be obscured by fluctuations in the baseline phase, missing data, and fewer randomization assignments, which afford more opportunities to detect a trend at the introduction of the treatment. CBT and exposure-based interventions typically demonstrate delayed effects as they target new learning which can take multiple treatment sessions to generate and consolidate. Future research might consider beginning the intervention only when the baseline phase reaches stabilization and including additional baseline randomization lengths, which would allow for clearer detection of a pattern of treatment effects at the start of the intervention, even if delayed.

While the above factors likely account for lack of significant findings, it is also important to consider how the specific questions used to assess daily measures contributed to our results. The treatment phase started with two-weeks of exposure therapy, which directly targets

avoidance behaviors by encouraging approach behaviors. Thus, one would assume an immediate increase in activity engagement at the start of treatment. The activity engagement daily measure focused primarily on how engaged participants were in their three most avoided activities. Our question assumes that not completing the activity on a given day is a reflection of avoidance, however, the question did not account for whether participants had the opportunity to complete the activity, which may partially explain lack of engagement. For example, numerous participants indicated avoiding school-related activities and sports-based practices. It is possible that on certain days of the week participants did not have the opportunity to complete these activities, thus ratings of "0" on the daily measure may reflect lack of opportunity rather than fear-based avoidance. Additionally, the activity engagement daily measure was idiographic, which prevented us from examining one activity at a time as not all participants indicated avoiding the same activities. Future studies might consider measuring how likely participants would be to avoid the activity if given the opportunity or the extent to which fears about their post-concussion symptoms might limit their engagement in activities to better capture avoidance. Additionally, a more standardized measure assessing avoidance on specific domains of activities (e.g., activities that require concentration, activities that require physical exertion, activities that involve socializing in loud contexts) would allow for more direct comparisons across participants and provide more specific examination of how the intervention influences avoidance in different domains of functioning.

Baseline stability is a critical component of multiple baseline designs. A few possible explanations can be offered for why the present sample largely did not demonstrate baseline stability in the daily measures. It is important to consider the potential reciprocal relationship between post-concussion symptoms, behavioral avoidance, and pain catastrophizing (Kay et al.,

1992). As we already established above, the activity engagement daily measure only assessed for engagement in each participant's 3 primary avoided activities. As such, we do not have a measure of how active participants were overall. Research suggests that increasing exercise (particularly if not gradual) following a period of inactivity can lead to an immediate increase in symptoms (e.g., Willer & Leddy, 2006). It is possible that daily variations in overall activity level influenced fluctuations in symptom severity in patients. Similarly, changes in symptom severity and activity engagement may have influenced the level of pain catastrophizing, such that an increase in symptoms following activity engagement caused participants to begin worrying about their symptoms (particularly during the baseline phase since they had not yet learned strategies to reinterpret symptoms and challenge unhelpful thoughts). Additionally, it is plausible that if participants did experience an increase in symptoms and catastrophizing following increases in activity, it may lead them to be less active in the following days, which may then result in lower levels of pain catastrophizing and symptom severity. In the present study, each daily measure was collected every three days to reduce patient burden, thus we are unable to examine daily correlations between the three daily measures. Future research would benefit from assessing each variable on a daily basis, as well as utilizing techniques to capture a more global measure of activity level to examine their reciprocal relationship and whether it contributes to fluctuations in each of the measures over time.

Daily measures were also analyzed using multilevel mixed effects models to examine changes over the treatment phase. Results revealed significant downward slopes in pain catastrophizing and post-concussion physical symptom. There was no significant association between treatment and the other daily measures. To examine whether reductions in post-concussion physical symptoms were explained by reductions in pain catastrophizing, we next

tested mediation. Results revealed that when pain catastrophizing was included in the model of physical symptoms regressed on time, time was no longer a significant predictor, suggesting mediation. However, bootstrapping procedures used to test the significance of the indirect effect suggest that mediation did not reach statistical significance. The present analyses had a small sample size (N = 9) thus, it is not surprising that results did not reach statistical significance. The detection of mediation, however, is promising, suggesting that interventions targeting pain catastrophizing can help to reduce post-concussion symptoms. This finding is consistent with the literature on chronic pain and other bodily distress syndromes, which shows that higher levels of pain catastrophizing is associated with increased pain ratings and interventions targeting pain catastrophizing help to reduce pain (e.g., Crombez et al., 2002; Leeuw et al., 2008; Thorn et al., 2007). In the present study, the measure of catastrophizing was specifically related to pain, which may explain why the measure appeared to be associated with only post-concussion physical symptoms. It is possible that a broader metric of thought catastrophizing may have better captured any associations between catastrophic thinking and post-concussion cognitive, emotional and sleep symptoms.

The battery of questionnaires collected at pre-treatment, post-treatment and 6-weeks follow-up aimed to capture treatment-related changes in the primary outcome variables (i.e., avoidance, pain catastrophizing, and post-concussion symptoms) as well as mood and anxiety symptoms, illness-related beliefs and attitudes, sleep quality and functioning. All treatment completers demonstrated reductions in avoidance at post-treatment, with improvements maintained at 6-weeks follow-up, suggesting that the intervention successfully reduced avoidance. The majority of participants showed improvements in all questionnaires at post-treatment. P3 showed worsening in the PSQI and post-concussion sleep symptoms of the PSQI;

P7 showed an increase in the RAAvI distress scale; P8 reported increases in the BAI, SDS and PSQI; and P9 showed mild increases in pain catastrophizing (PCS) and post-concussion symptoms total (PCSI-13R; driven by a large increase in physical symptoms). Each of these participants except for P3 completed the subset of questionnaires at 6-follow-up, which reflected overall improvements in the RAAvI avoidance and distress scales, PCS and the PCSI-13R from pre-treatment, suggesting overall improvements in avoidance, pain catastrophizing and post-concussion symptoms from pre-treatment to follow-up. P6 was the only participant to show improvements in all questionnaires at post-treatment, and improvements from pre-treatment were maintained at 6-weeks follow-up.

P4 demonstrated the most symptom worsening of all participants in her post-treatment questionnaires, however, this is likely due to the fact that P4 was unable to complete the treatment and her post-treatment measures represent mid-treatment scores. Interestingly, P4 reported decreases in both the RAAvI avoidance and distress scales and PCS scores, suggesting that the intervention effectively reduced avoidance and pain-catastrophizing by mid-treatment (i.e., the exposure module). She reported increased post-concussion symptoms, however, which may be explained by the natural increase in symptoms that can occur when increasing exercise amount following a period of inactivity, particularly if exercise increase is not gradual (Willer & Leddy, 2006). It is possible that P4 would have experienced a decrease in post-concussion symptoms by the end of the treatment with additional time to recondition and reach symptom resolution. Utilizing devices to measure activity-related symptom changes, such as biofeedback devices during activity engagement to measure ANS changes and ecological momentary assessment (EMA) to measure self-reported symptoms, may help to isolate effects of graded activity increase on symptoms.

Paired samples t-tests were conducted to examine changes from pre-treatment to post-treatment and post-treatment to 6-weeks follow-up at the group level (N = 6). Results revealed significant reductions from pre- to post-treatment in the RAAvI avoidance and distress scales, PCS and the BIPQ. Taken with the individual questionnaire results, these findings suggest that the treatment effectively targets and reduces avoidance, pain catastrophizing and other illness-related beliefs. No differences were observed between measures at post-treatment and 6-weeks follow-up, which might suggest that observed improvements from pre- to post-treatment were maintained. Given the individual reductions observed in the other measures, it is likely that non-significant t-tests reflect issues of statistical power rather than lack of improvement. In fact, examination of the means for each measure demonstrated improvements on all measures at post-treatment. Of all the questionnaires, the PSQI demonstrated the smallest mean difference from pre- to post-treatment. This is likely explained by the four participants who showed increases in the PSQI at post-treatment. This finding is particularly interesting given that the post-concussion sleep daily measure was the only measure to demonstrate significant reductions from the baseline to the treatment phase. It is important to note that the post-concussion sleep symptom daily measure and the PSQI capture different elements of sleep. The PSQI is a measure of sleep quality and efficiency over the previous month, whereas the post-concussion sleep symptom daily measure is an assessment of how bothered individuals were by difficulty sleeping and feelings of fatigue in the previous 24 hours. The sleep symptom daily measure captures only a portion of the PSQI, thus, it is possible that participants might report improvements in daily feelings of fatigue and difficulty sleeping even if they report unchanged or worse overall sleep quality. Further, it should be noted that for the participants who demonstrated increases in the PSQI at post-treatment, scores only improved by 1-5 points from pre-treatment, reflecting a

minor difference. Additionally, the CBT + CART treatment does not include any interventions typically used to improve sleep quality thus, it is not surprising that the intervention may have been less effective for reducing the PSQI. Fatigue and difficulty sleeping are non-specific symptoms of concussions and improvements over treatment likely reflect overall post-concussion symptom reduction as a result of treatment.

Participants engaged in CART during the last 4-weeks of the 6-week intervention. $EtCO_2$ and PR were collected as measures of ANS functioning. The capnometer also captured RR and SpO_2, which participants used to guide breathing practices (i.e., RR guided paced breathing; SpO_2 levels provided reassurance to participants that they were breathing enough air even if they experienced symptoms of breathlessness). The present study examined ANS functioning at rest, thus, only the baseline phase of the CART practices was examined. Six participants engaged in CART and the number of practices during the treatment ranged from 7 to 46 practices across 6 to 24 days, suggesting high variability of treatment compliance in the sample. $EtCO_2$, PR, RR and SpO_2 were graphed for each participant to examine changes over time. P8 demonstrated an upward trend over the course of CART, increasing his $EtCO_2$ at rest from 28 mmHg at his first practice to 37 mmHg at his final practice, suggesting normalization of $EtCO_2$. The other participants had more variability in their resting $EtCO_2$ and did not indicate clear treatment effects. P6 and P7 demonstrated mild increases in PR over the course of CART, which is contrary to hypotheses which expected CART to lower resting PR with ANS normalization. It should be noted that CART is specifically designed to alter CO_2 levels (Meuret et al., 2009; Meuret et al., 2010). Thus, as a measure of ANS functioning, we might see reductions in PR among individuals who demonstrate normalization of $EtCO_2$ after CART. However, it is not surprising that P6 and P7 did not show reductions in PR after CART without also demonstrating

normalization in $EtCO_2$ (which they did not). Other participants did not demonstrate treatment effects on PR levels. Multilevel mixed effects analyses were used to examine how $EtCO_2$ and PR changed over time at the group level. Consistent with the visual inspection, results suggest no effect of CART on $EtCO_2$ and PR. Because there was no effect of CART on these variables, follow-up analyses examining whether ANS normalization mediated effects of treatment on post-concussion symptoms were not tested. Future analyses with a larger sample size might explore how $EtCO_2$ and PR covary with daily measures over time, specifically post-concussion symptoms.

In a study conducted by our group comparing PPCS patients (including some overlap with the current sample) to healthy controls during an in-person experimental paradigm examining autonomic functioning at rest and in response to a stressor, PPCS patients demonstrated mild hypocapnia at rest (Snyder et al., 2021). Of the six participants in the present study who completed CART, four were hypocapnic during the baseline phase of their first CART practice (i.e., prior to learning any breathing-related skills), suggesting that hypocapnia might be a marker of PPCS. P3 and P6 demonstrated $EtCO_2$ levels in the normal range at their first CART practice and $EtCO_2$ remained largely in the normal range throughout CART. P3 and P6 also demonstrated increases in activity engagement from baseline to the treatment phase. It is possible that $EtCO_2$ levels were impacted by increases in activity levels, particularly exercise, throughout the first two weeks of the treatment phase. This explanation is supported by the literature that suggests that prolonged rest can exacerbate post-concussion ANS dysfunction and lead to deconditioning and additional symptoms (e.g., fatigue, depression; Leddy et al., 2007). Additionally, consistent aerobic exercise is beneficial for increasing parasympathetic activity, increasing cerebral blood flow, and improving ANS regulation, such as HRV (Leddy et al.,

2007), and graded exercise interventions have been found to normalize altered ANS and improve symptoms in patients with PPCS (Leddy et al., 2010; Leddy et al., 2018). Without a pre-treatment measure of ANS functioning, however, we cannot conclude whether the first two weeks of exposure therapy impacted $EtCO_2$ levels. Additional research comparing effects of exposure-related exercise engagement versus CART on $EtCO_2$ and other measures of ANS functioning may help to elucidate which intervention components have the greatest impact on ANS functioning in PPCS. The results could have important implications for treatment accessibility and dissemination, as an intervention not requiring biofeedback equipment is more easily disseminated.

The present study is the first to examine CART on ANS functioning for individuals with PPCS. Previous research supports the benefits of CART for normalizing hypocapnic $EtCO_2$ levels in anxious samples (Meuret et al., 2009; Meuret et al., 2010). A full course of CART involves twice daily practices for 4-weeks (i.e., 56 practices total). In the present sample, participants were not adherent to the recommended treatment dose. P6 was the only participant who engaged in consistent twice daily CART practices, however, her resting $EtCO_2$ levels were already in the normal range at the start of CART and did not demonstrate changes over time. P8 was the second most consistent at CART practice and the only participant who demonstrated expected resting $EtCO_2$ normalization by the end CART. It is possible that more participants would have demonstrated $EtCO_2$ normalization with more consistent practice. Future research with larger sample sizes would allow for analyses to control for the number of practices and performance during the pacing and transition phases on changes at rest over time.

To date, no gold standard treatment exists for PPCS. Our study builds off the small literature in support of psychological interventions for PPCS by proposing a theoretical

biopsychosocial model of PPCS and testing the efficacy of a novel home-based CBT intervention. Our findings lend support for the benefits of CBT for PPCS by reducing avoidance behaviors, pain catastrophizing and post-concussion symptoms. The study also tested whether incorporating a biofeedback CART intervention normalizes PPCS-related ANS dysregulation (as measured by $EtCO_2$ and PR). By proposing a theoretical model and designing an intervention to target the factors hypothesized to underly PPCS, our study contributes to the literature by highlighting factors that might identify individuals at risk of developing PPCS following a concussion, as well as those most likely to respond to CBT-based interventions.

Limitations and Future Directions

The present study has a few limitations. First, the study used two randomization baseline lengths, which reduced power for the multiple baseline design to detect intervention effects. In the present study, participants were experiencing distressing functional impairment that necessitated the initiation of treatment as soon as possible. Future research utilizing multiple baseline designs might consider incorporating additional baseline lengths up to the full-length of the treatment (i.e., 6-weeks) to increase confidence that changes in the daily measures during the treatment phase are due to the intervention rather than the passage of time. In regard to the follow-up group-level analyses (i.e., multilevel mixed effects and paired-sample t-tests), power was reduced by the small sample size. Lastly, although the activity engagement daily measure intended to capture avoidance, it did not account for whether participants had the opportunity to complete their three most avoided activities on a given day, which may partially explain lack of engagement. With a more precise daily measure of avoidance our study may have been able to detect significant reductions in avoidance behaviors in the randomization tests, consistent with

the observed reductions in the RAAvI from pre- to post-treatment. Future research would benefit from utilizing a more specific and standardized measure of avoidance.

Despite these limitations, the results of the pilot study are promising and have important implications for the treatment of PPCS. A strength of the present study is that the intervention was able to be completed from home, which increased treatment accessibility. However, because the intervention was largely self-guided, we are unable to monitor participant compliance and skills acquisition during the treatment. Future directions of this work include identifying strategies to increase intervention feasibility and scalability. The increase of digital interventions in recent years provides a promising option. Developing a digital version of the intervention that compiles all the materials in one location (e.g., daily measures, treatment manual, homework practices) would reduce patient burden and likely improve compliance with the intervention. Additionally, a digital self-guided version of the intervention would increase accessibility and scalability by reducing the need for trained clinicians to guide the intervention. Future work identifying the most effective components of the intervention is also warranted. For example, conducting an RCT comparing CBT (i.e., exposure and cognitive restructuring) to CBT + CART for PPCS would provide important information on whether CART is necessary for treatment improvements and if exposure is able to normalize ANS functioning. A digital version of the intervention that does not require biofeedback equipment would allow for easier dissemination.

Conclusion

In sum, this pilot study demonstrates that CBT may be a beneficial intervention for reducing avoidance, pain catastrophizing, and post-concussion symptoms in individuals experiencing PPCS. Specifically, we found evidence that our intervention effectively targets avoidance and pain catastrophizing and reduces post-concussion symptoms. Further, tests of

mediation suggest that targeting pain catastrophizing may help to resolve physical symptoms of PPCS, although results must be interpreted with caution as the indirect effect did not meet statistical significance. Our findings provide support for a fear-avoidance model of PPCS. Further, the data collected via capnometry add to the literature of ANS dysregulation in PPCS by demonstrating hypocapnia at rest in our sample. Although our study did not demonstrate ANS normalization across participants (and subsequent post-concussion symptom resolution) as a result of our intervention, we have some support that consistent CART practice may normalize hypocapnic resting $EtCO_2$ levels (i.e., P8). Additional research examining the associations between resting $EtCO_2$ and post-concussion symptoms and interventions to target ANS dysregulation in PPCS is needed to better understand the relation between ANS and PPCS. Our findings have potential implications for identifying patients most likely to respond to CBT, helping patients with PPCS return to prior functioning and reducing the economic burden of PPCS by offering an accessible and scalable intervention. Continued research examining the benefits of CBT and CART for PPCS is essential to identify effective interventions for this largely untreated population.

Table 1. *Sample demographics and characteristics*

	PPCS Sample (n = 9)
Sex	
Male (n)	2
Female (n)	7
Age (years)	16.33 (2.45)
Education completed (years)	9.89 (2.57)
Medical History	
Migraine (yes)	3
Depression (yes)	2
Anxiety (yes)	4
Other psychiatric diagnosis (yes)	0
Taking medication (yes)	7
Number of diagnosed concussions	1.89 (1.17)
Days since most recent injury	146 (81.22)

Note: Values are presented in mean (SD) unless otherwise noted.

Table 2. *Pre-treatment questionnaire descriptives and correlation coefficients*

Variable	RAAvI-A	RAAvI-D	PCS	PCSI	BAI	BDI-II	BIPQ	SDS	PSQI
RAAvI-A	1	--	--	--	--	--	--	--	--
RAAvI-D	.66	1	--	--	--	--	--	--	--
PCS	.41	.06	1	--	--	--	--	--	--
PCSI	.37	-.21	.26	1	--	--	--	--	--
BAI	.38	-.10	.48	.23	1	--	--	--	--
BDI-II	.59	.06	.86**	.51	.62	1	--	--	--
BIPQ	.04	.01	.23	-.22	-.01	.02	1	--	--
SDS	.60	.90**	.16	-.02	-.05	.19	.18	1	--
PSQI	.73*	.49	.49	.53	.16	.48	.41	.62	1
M	6.5	7.25	22.56	49.22	12.67	18.78	47.56	17.44	9.44
SD	2.14	2.32	7.96	23.19	7.68	7.0	11.52	7.3	3.71

Note: Pearson's correlations (R); RAAvI-A = Return to Activity Avoidance Inventory-Avoidance; RAAvI-D = Return to Activity Avoidance Inventory-Distress; PCS = Pain Catastrophizing Scale; PCSI = Post-Concussion Symptom Inventory (total); BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory-II; BIPQ = Brief Illness Perception Questionnaire; SDS = Sheehan Disability Scale; PSQI = Pittsburgh Sleep Quality Index.
N = 9; * p-value < 0.05, ** p-value < 0.01

Table 3. *Post-treatment questionnaire descriptives and correlation coefficients*

Variable	RAAvI-A	RAAvI-D	PCS	PCSI	BAI	BDI-II	BIPQ	SDS	PSQI
RAAvI-A	1	--	--	--	--	--	--	--	--
RAAvI-D	.95**	1	--	--	--	--	--	--	--
PCS	.76	.79	1	--	--	--	--	--	--
PCSI	.17	.43	.06	1	--	--	--	--	--
BAI	.22	.45	.49	.54	1	--	--	--	--
BDI-II	-.09	.15	-.09	.86*	.25	1	--	--	--
BIPQ	.74	.53	.27	-.28	-.25	-.48	1	--	--
SDS	.66	.42	.35	-.53	-.28	-.68	.95**	1	--
PSQI	.19	.25	-.36	.67	-.15	.60	.21	-.09	1
M	3	4.33	13.33	38.67	8.83	13.67	37.50	16.33	9
SD	3.29	2.94	10.88	17.29	6.94	7.87	12.82	8.62	6.45

Note: Pearson's correlations (R); RAAvI-A = Return to Activity Avoidance Inventory-Avoidance; RAAvI-D = Return to Activity Avoidance Inventory-Distress; PCS = Pain Catastrophizing Scale; PCSI = Post-Concussion Symptom Inventory (total); BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory-II; BIPQ = Brief Illness Perception Questionnaire; SDS = Sheehan Disability Scale; PSQI = Pittsburgh Sleep Quality Index.
N = 6; * p-value < 0.05, ** p-value < 0.01

Table 4. *Six-weeks post-treatment questionnaire descriptives and correlation coefficients*

Variable	RAAvI-A	RAAvI-D	PCS	PCSI
RAAvI-A	1	--	--	--
RAAvI-D	.83	1	--	--
PCS	-.69	-.41	1	--
PCSI	-.43	-.70	-.36	1
M	4	3.75	3.33	20.3
SD	1.83	2.87	4.93	14.01

Note: Pearson's correlations (R); RAAvI-A = Return to Activity Avoidance Inventory-Avoidance; RAAvI-D = Return to Activity Avoidance Inventory-Distress; PCS = Pain Catastrophizing Scale; PCSI = Post-Concussion Symptom Inventory (total).
N = 4

Table 5. *Pre- vs. post-treatment paired samples t-test results*

	M (SD)	t-statistic	df	p-value
Return to Activity Avoidance Inventory				
Avoidance	4.0 (2.53)	3.87	5	0.01*
Distress	3.67 (3.45)	2.61	5	0.048*
Pain Catastrophizing Scale	8.83 (8.04)	2.69	5	0.04*
Post-Concussion Symptom Inventory - Total	13.17 (22.83)	1.41	5	0.22
Physical	6.50 (9.73)	1.63	5	1.65
Emotional	1.50 (5.93)	0.62	5	0.56
Cognitive	5.17 (8.01)	1.58	5	0.18
Sleep	.001 (3.63)	0.00	5	1.00
Beck Anxiety Inventory	5.50 (5.68)	2.37	5	0.06
Beck Depression Inventory-II	5.83 (8.28)	1.73	5	0.15
Brief Illness Perception Questionnaire	11.0 (8.25)	3.27	5	0.02*
Sheehan Disability Scale	4.50 (5.17)	2.13	5	0.09
Pittsburgh Sleep Quality Index	1.67 (6.25)	0.65	5	0.54

Note: M (SD) represent paired differences
N = 6; * p-value < 0.05

Table 6. *Post-treatment vs. 6-week follow-up paired samples t-test results*

	M (SD)	t-statistic	df	p-value
Return to Activity Avoidance Inventory*				
Avoidance	0.50 (1.29)	0.78	3	0.50
Distress	1.50 (1.73)	1.73	3	0.18
Pain Catastrophizing Scale**	5.33 (5.77)	1.60	2	0.25
Post-Concussion Symptom Inventory – Total**	13.0 (29.46)	0.76	2	0.52
Physical	1.67 (8.08)	0.36	2	0.76
Emotional	4.0 (7.81)	0.89	2	0.47
Cognitive	5.0 (8.72)	0.99	2	0.43
Sleep	2.33 (4.93)	0.82	2	0.50

Note: M (SD) represent paired differences

*N = 4

**N = 3

Table 7. *Individual percent change in pre- and post-treatment questionnaire scores (completers)*

Participant	Questionnaire	Pre-treatment	Post-treatment	% Change
P3	RAAvI Avoidance	8	0	-100%
	RAAvi Distress	8	3	-63%
	PCS	18	8	-56%
	PCSI	61	58	-5%
	Physical	23	18	-22%
	Emotional	6	6	0%
	Cognitive	24	19	-21%
	Sleep	8	15	88%
	BAI	22	16	-27%
	BDI-II	20	20	0%
	BIPQ	27	18	-33%
	SDS	15	2	-87%
	PSQI	8	10	25%
P4	RAAvI Avoidance	3	0	-100%
	RAAvi Distress	6	2	-67%
	PCS	16	12	-25%
	PCSI	16	34	113%
	Physical	7	7	0%
	Emotional	7	16	129%
	Cognitive	2	11	450%
	Sleep	0	0	0%
	BAI	14	7	-50%
	BDI-II	13	19	46%
	BIPQ	50	25	-50%
	SDS	16	10	-38%

	PSQI	4	5	25%
P6	RAAvI Avoidance	7	2	-71%
	RAAvi Distress	11	2	-82%
	PCS	19	11	-42%
	PCSI	29	11	-62%
	Physical	13	9	-31%
	Emotional	2	1	-50%
	Cognitive	12	1	-92%
	Sleep	2	0	-100%
	BAI	2	0	-100%
	BDI-II	11	2	-82%
	BIPQ	53	41	-23%
	SDS	28	22	-21%
	PSQI	13	3	-77%
P7	RAAvI Avoidance	7	6	-14%
	RAAvi Distress	6	7	17%
	PCS	36	13	-64%
	PCSI	91	56	-38%
	Physical	31	15	-52%
	Emotional	20	13	-35%
	Cognitive	28	19	-32%
	Sleep	12	9	-25%
	BAI	19	4	-79%
	BDI-II	31	22	-29%
	BIPQ	50	46	-8%
	SDS	19	18	-5%
	PSQI	15	20	33%
P8	RAAvI Avoidance	7	2	-71%

	RAAvi Distress	7	3	-57%
	PCS	11	2	-82%
	PCSI	75	33	-56%
	Physical	25	5	-80%
	Emotional	16	9	-44%
	Cognitive	25	12	-52%
	Sleep	9	7	-22%
	BAI	6	8	33%
	BDI-II	14	9	-36%
	BIPQ	50	48	-4%
	SDS	20	22	10%
	PSQI	11	12	9%
P9	RAAvI Avoidance	10	8	-20%
	RAAvi Distress	10	9	-10%
	PCS	33	34	3%
	PCSI	39	40	3%
	Physical	16	22	38%
	Emotional	9	6	-33%
	Cognitive	13	11	-15%
	Sleep	1	1	0%
	BAI	23	18	-22%
	BDI-II	28	10	-64%
	BIPQ	61	47	-23%
	SDS	27	24	-11%
	PSQI	13	4	-69%

Table 8. *Individual percent change in pre-, post-treatment and follow-up questionnaire scores (completers)*

Participant	Questionnaire	Pre-treatment	Post-treatment	Follow-up	% Change (post – follow-up)	% Change total (pre – follow-up)
P6	RAAvI Avoidance	7	2	2	0%	-71%
	RAAvi Distress	11	2	2	0%	-82%
	PCS	19	11	9	-18%	-53%
	PCSI	29	11	16	45%	-45%
	Physical	13	9	12	33%	-8%
	Emotional	2	1	1	0%	-50%
	Cognitive	12	1	2	100%	-83%
	Sleep	2	0	1	100%	-50%
P7	RAAvI Avoidance	7	6	5	-17%	-29%
	RAAvi Distress	6	7	3	-57%	-50%
	PCS	36	13	1	-92%	-97%
	PCSI	91	56	9	-84%	-90%
	Physical	31	15	4	-73%	-87%
	Emotional	20	13	0	-100%	-100%
	Cognitive	28	19	4	-79%	-86%
	Sleep	12	9	1	-89%	-92%
P8	RAAvI Avoidance	7	2	3	50%	-57%
	RAAvi Distress	7	3	2	-33%	-71%
	PCS	11	2	0	-100%	-100%
	PCSI	75	33	36	9%	-52%
	Physical	25	5	8	60%	-68%
	Emotional	16	9	10	11%	-38%
	Cognitive	25	12	11	-8%	-56%
	Sleep	9	7	7	0%	-22%
P9	RAAvI Avoidance	10	8	6	-25%	-40%

RAAvi Distress	10	9	8	-11%	-20%

Figure 1. *Study Flow*

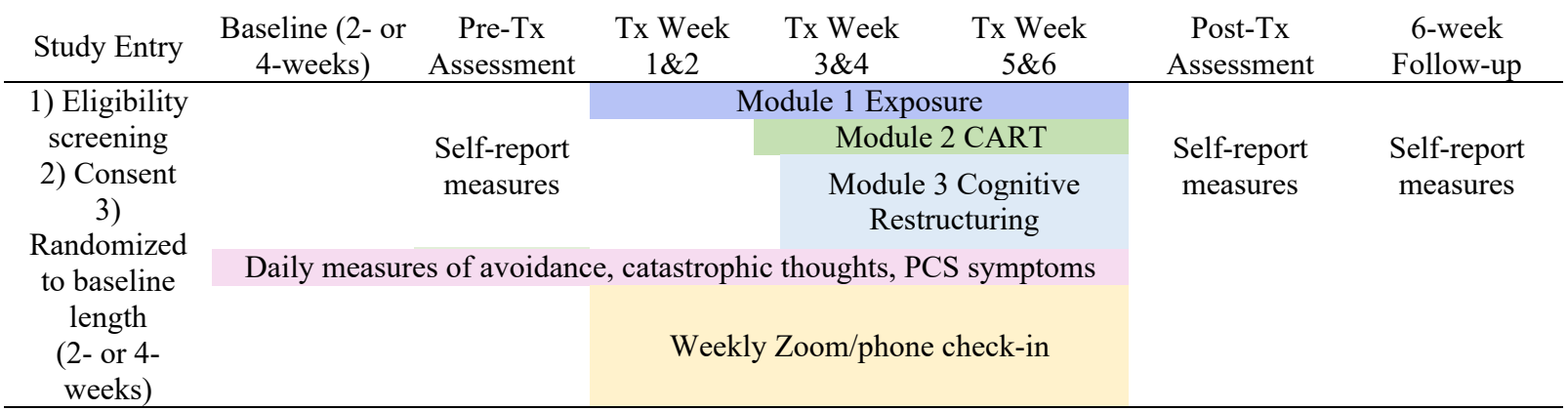


Figure 2a-d. *Participant 3 Daily Measures Scores Across Multiple-baseline Design (MBD) Phase*

Figure 2a

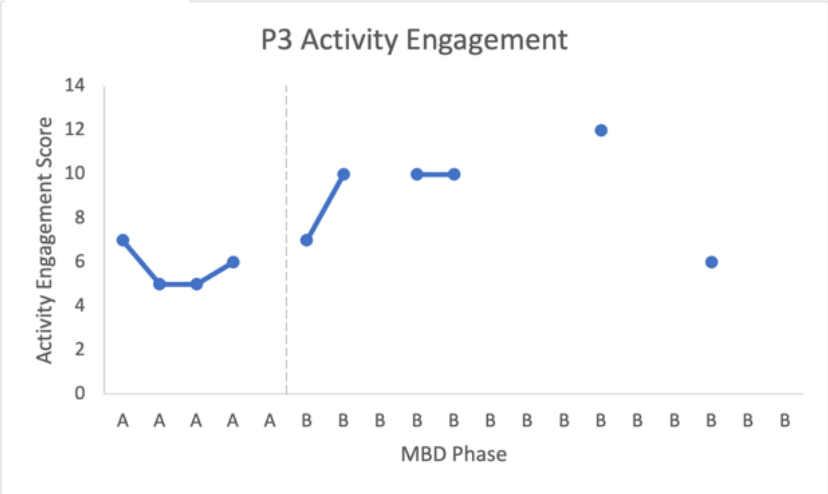


Figure 2b

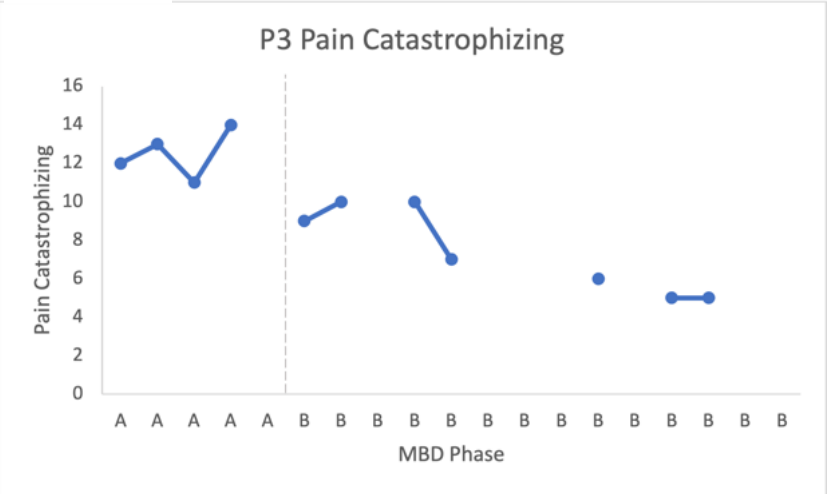


Figure 2c

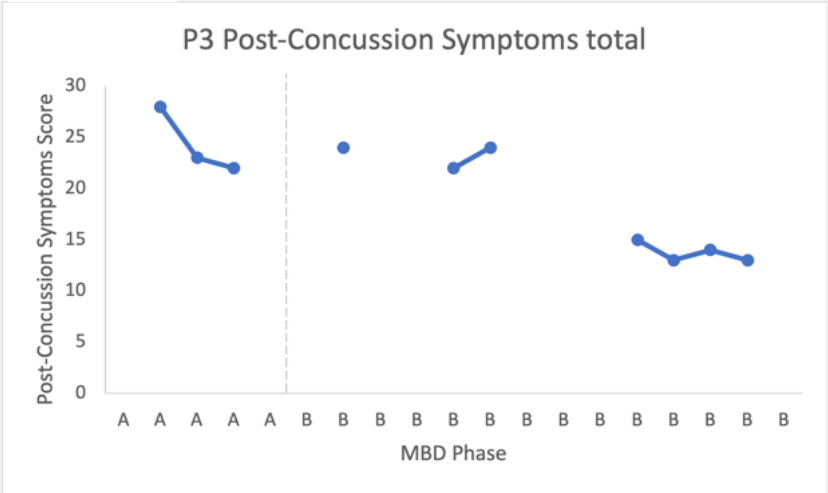


Figure 2d

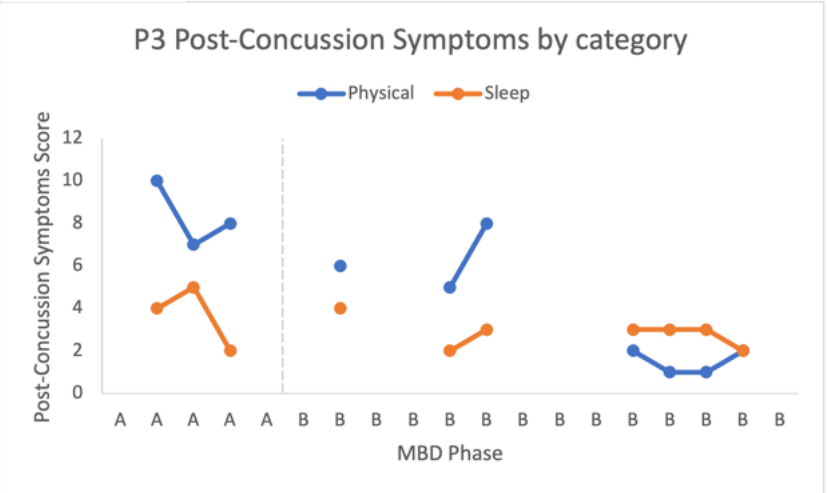


Figure 3a-d. *Participant 3 ANS Measures Across CART*

Figure 3a

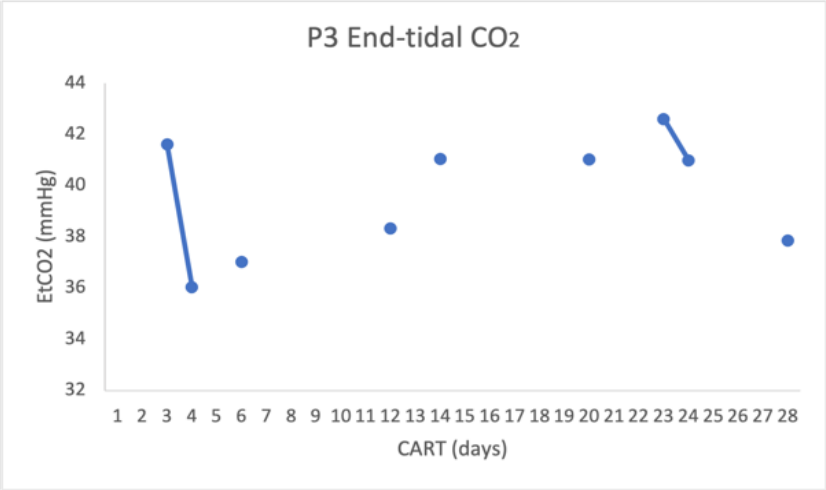


Figure 3b

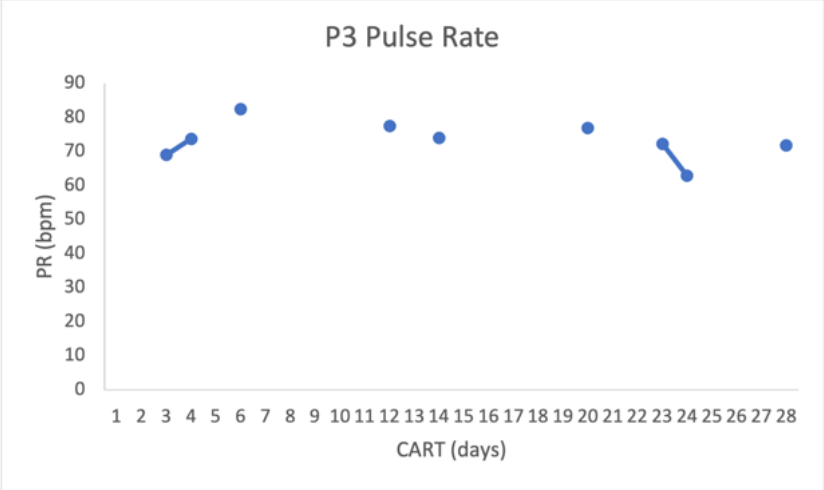


Figure 3c

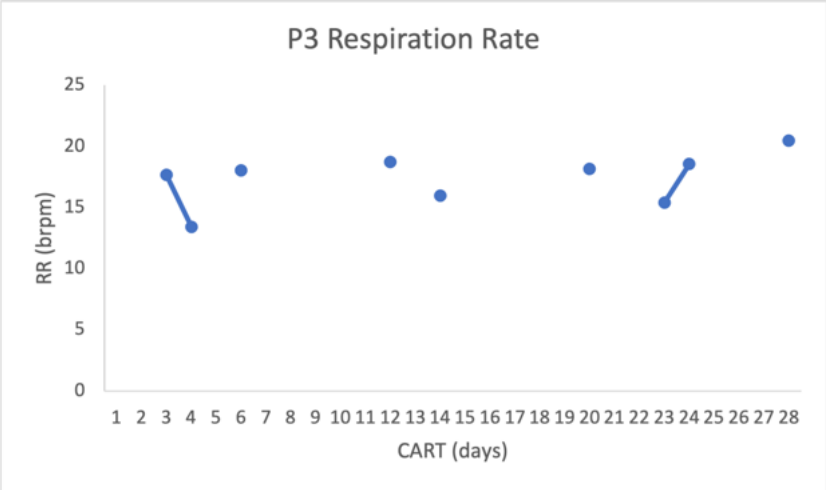


Figure 3d

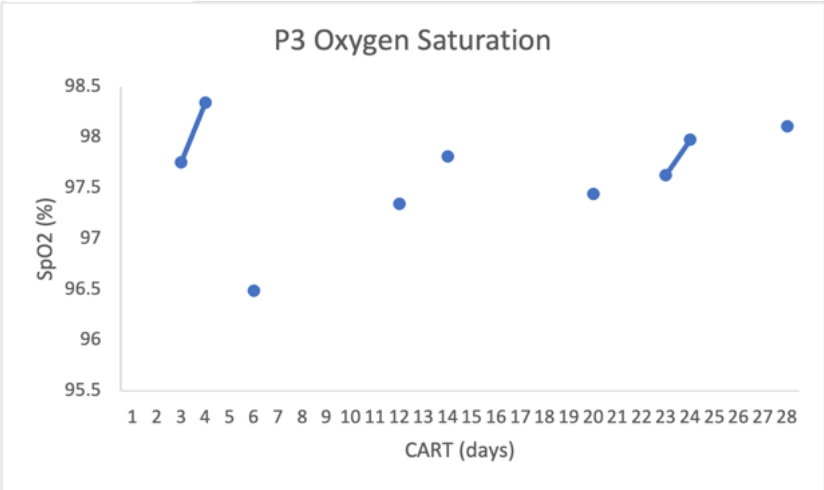


Figure 4a-d. *Participant 6 Daily Measures Scores Across Multiple-baseline Design (MBD) Phase*

Figure 4a

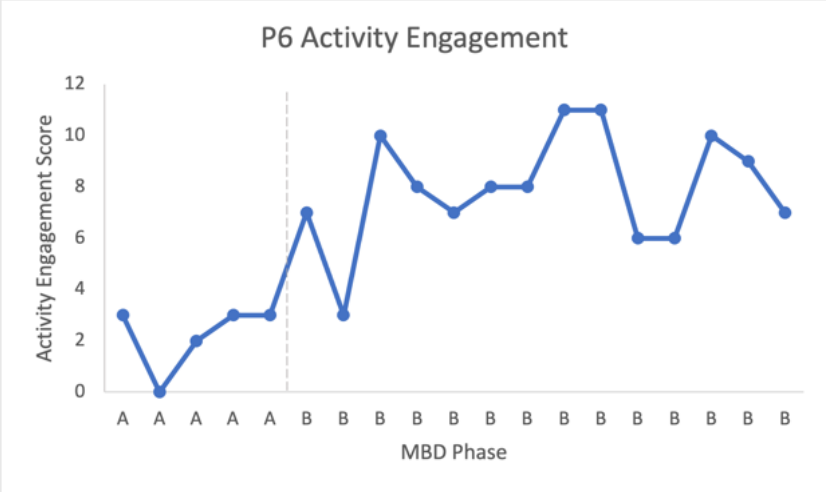


Figure 4b

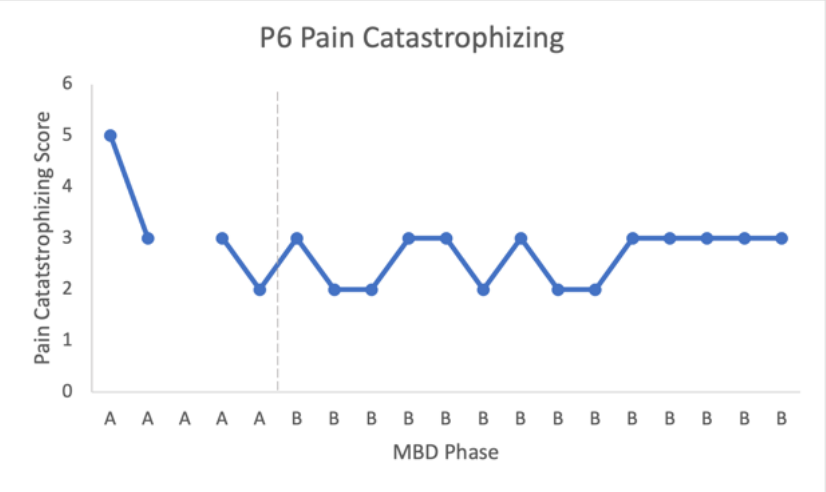


Figure 4c

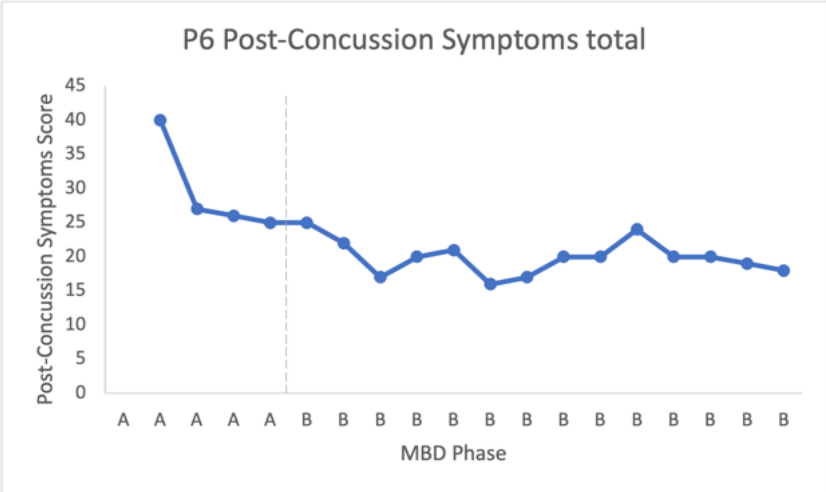


Figure 4d

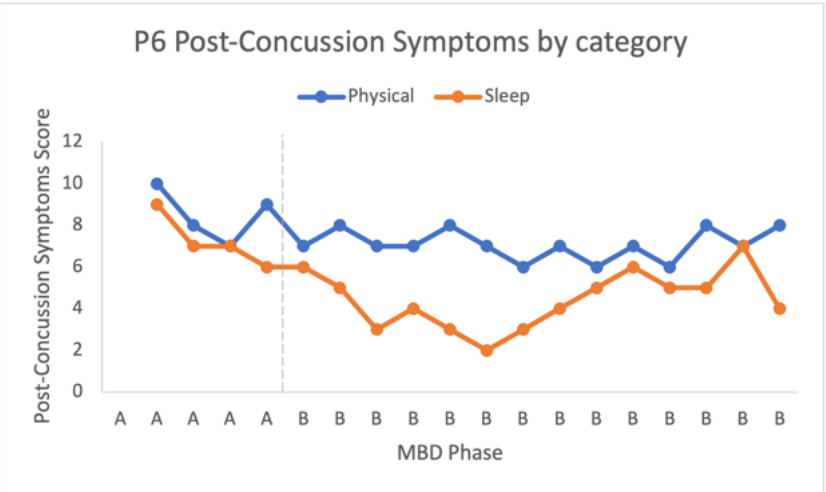


Figure 5a-d. *Participant 6 ANS Measures Across CART*

Figure 5a

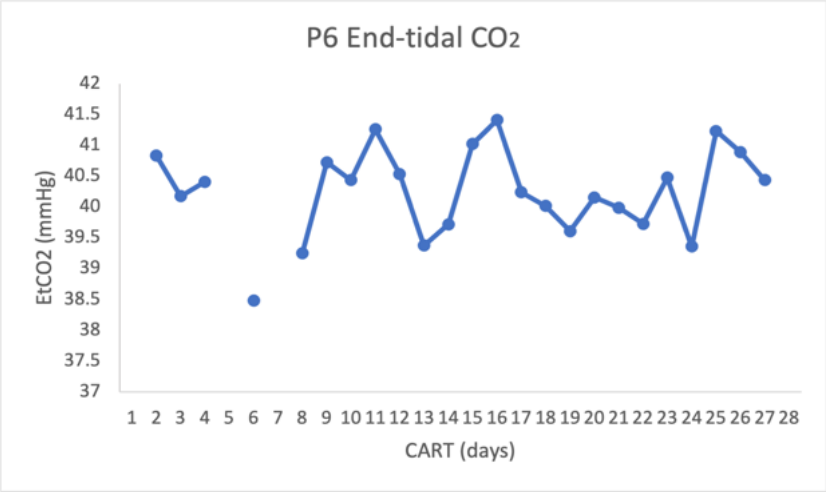


Figure 5b

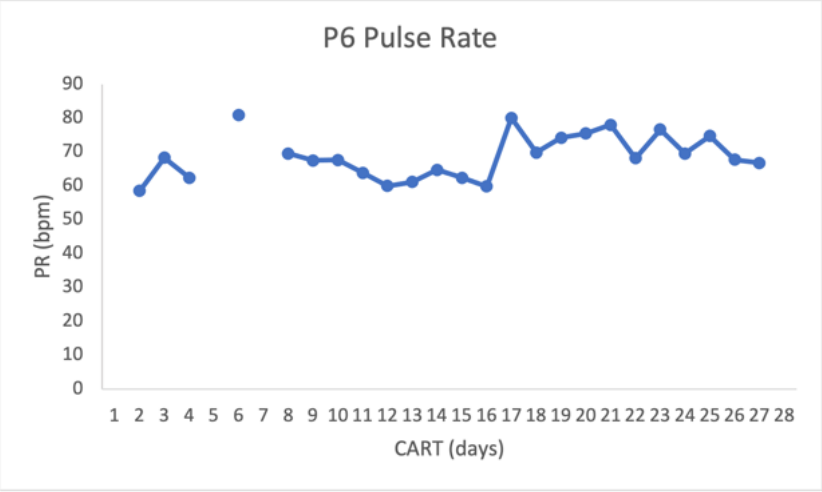


Figure 5c

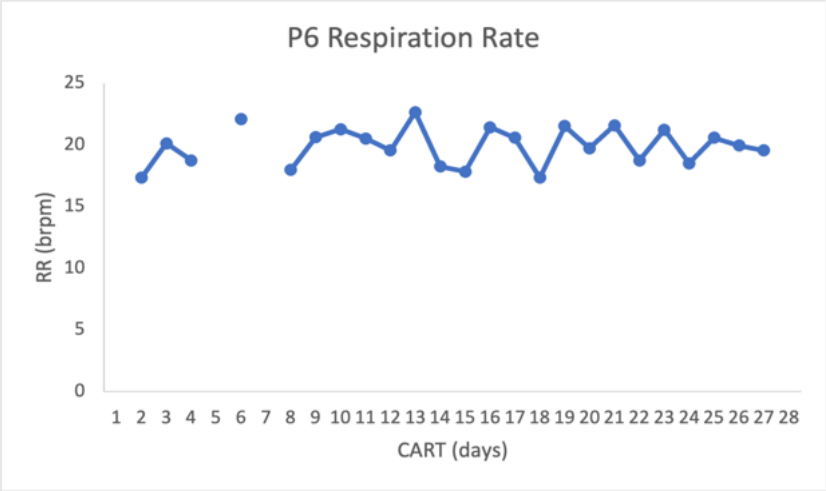


Figure 5d

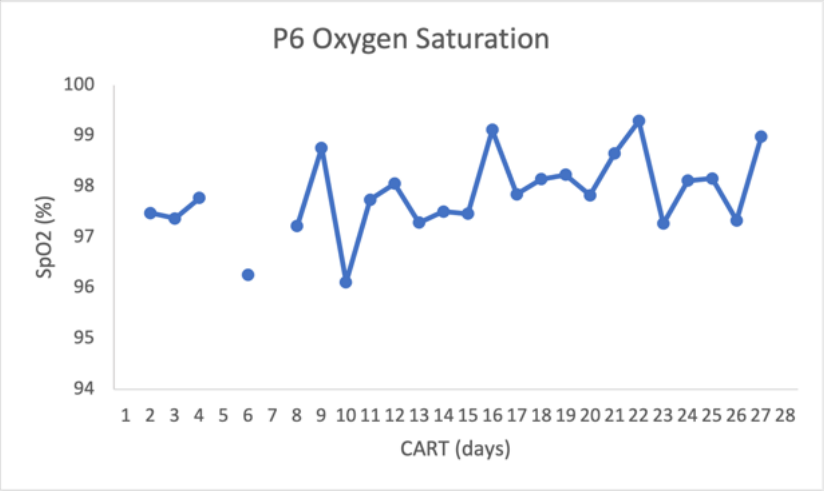


Figure 6a-d. *Participant 7 Daily Measures Scores Across Multiple-baseline Design (MBD) Phase*

Figure 6a

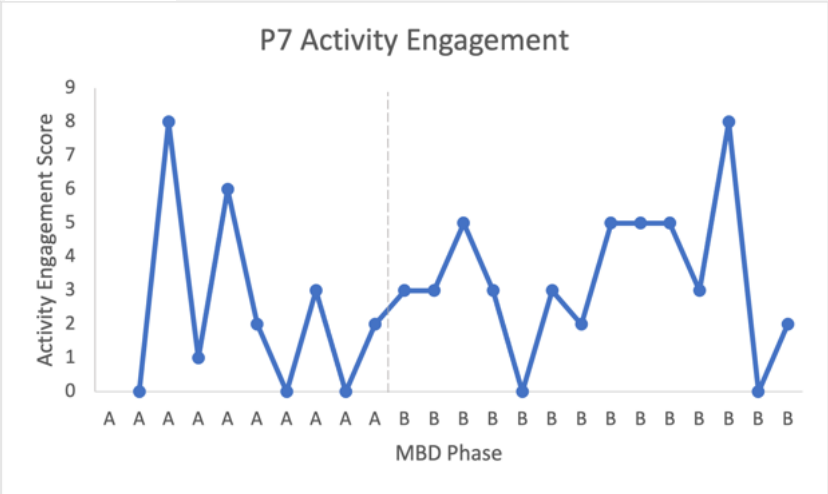


Figure 6b

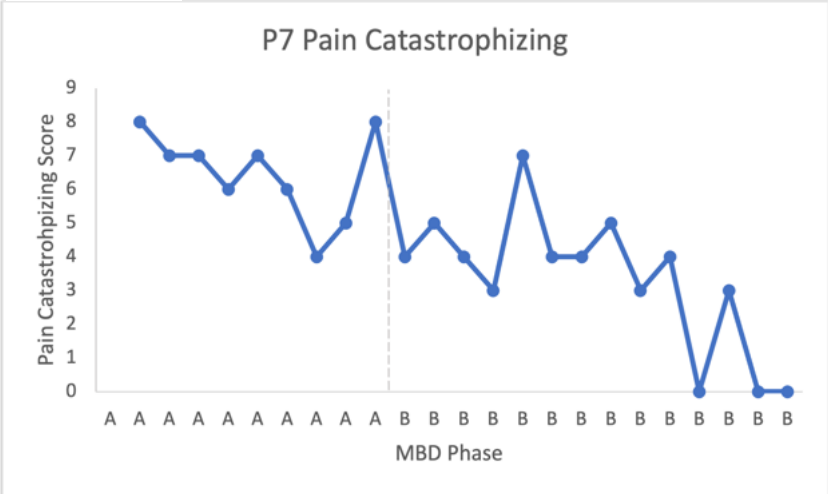


Figure 6c

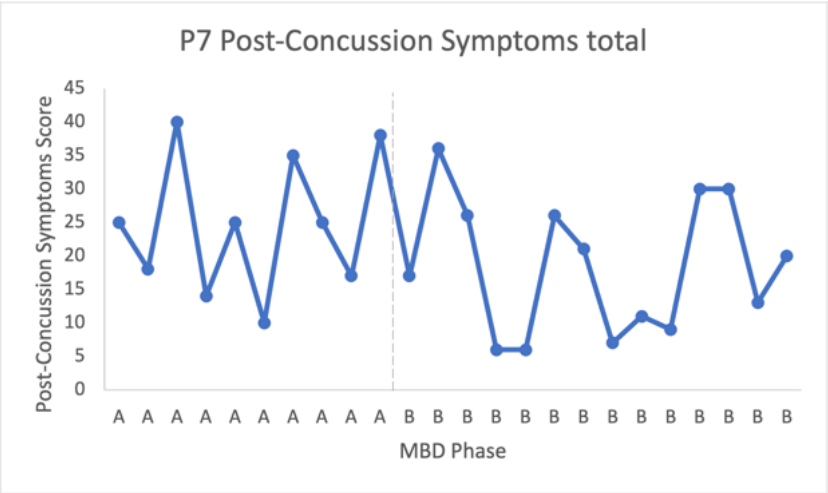


Figure 6d

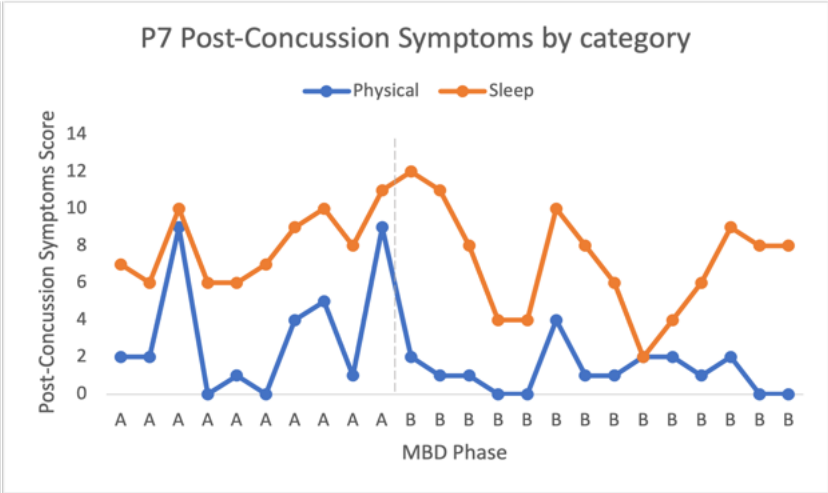


Figure 7a-d. *Participant 7 ANS Measures Across CART*

Figure 7a

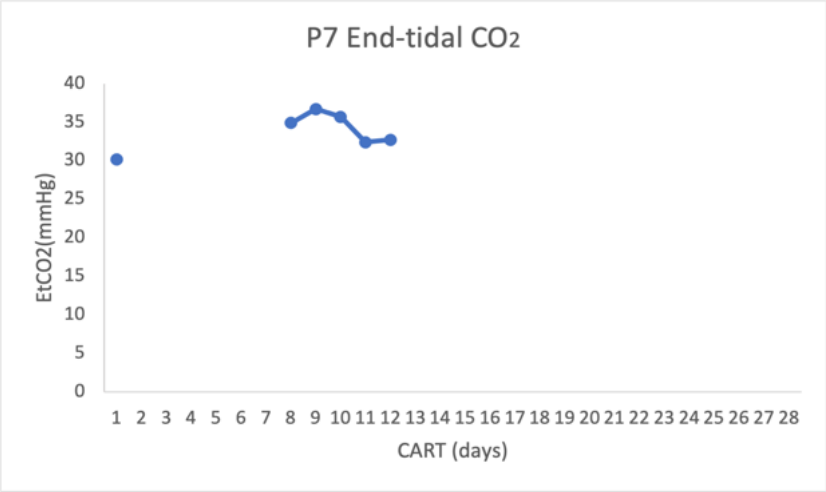


Figure 7b

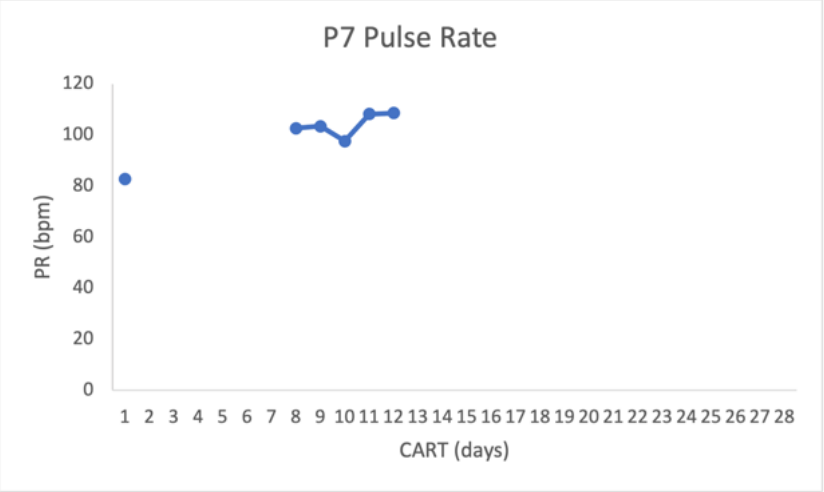


Figure 7c

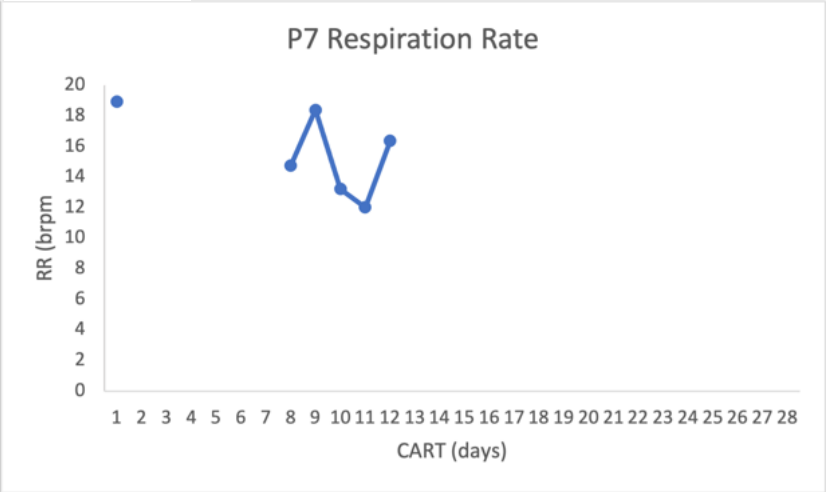


Figure 7d

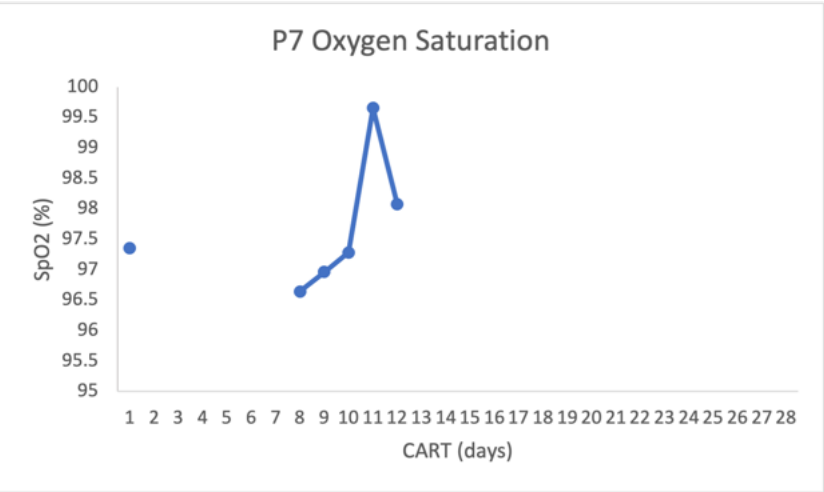


Figure 8a-d. *Participant 8 Daily Measures Scores Across Multiple-baseline Design (MBD) Phase*

Figure 8a

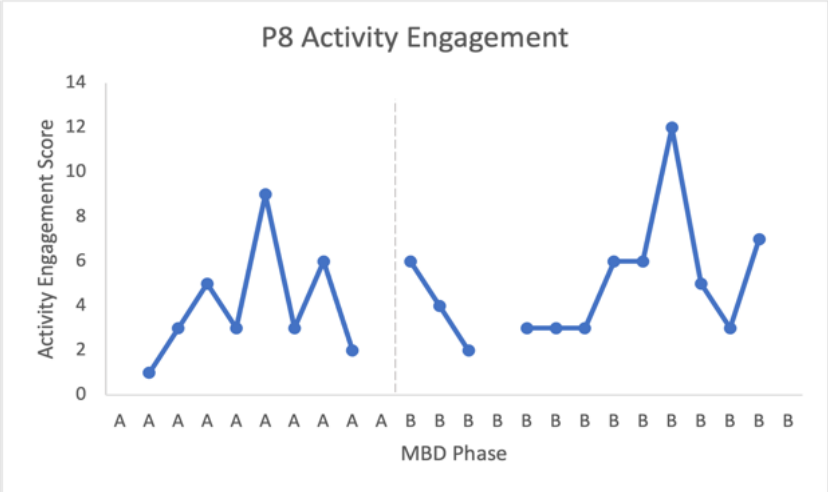


Figure 8b

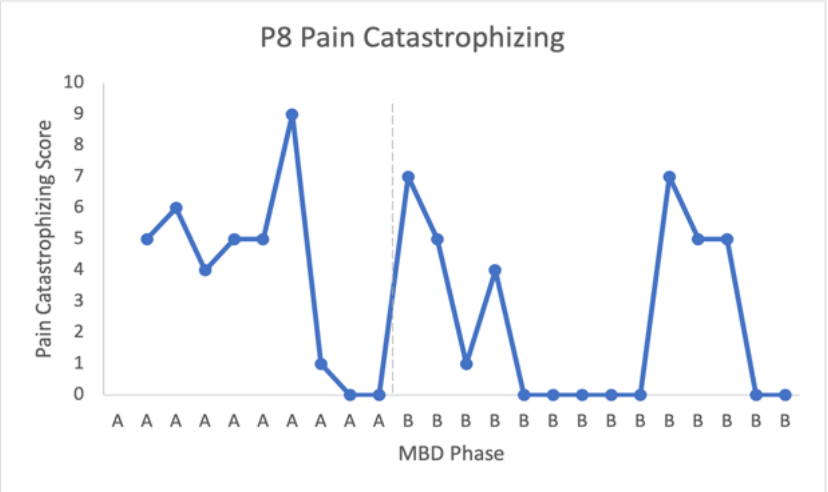


Figure 8c

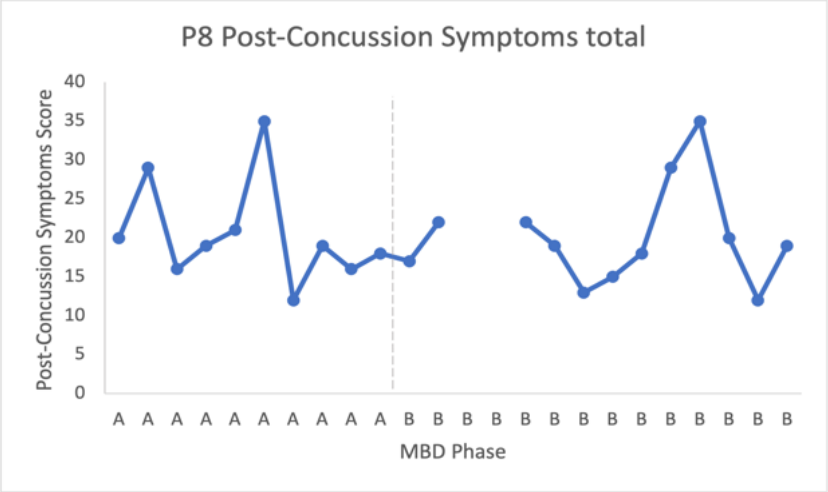


Figure 8d

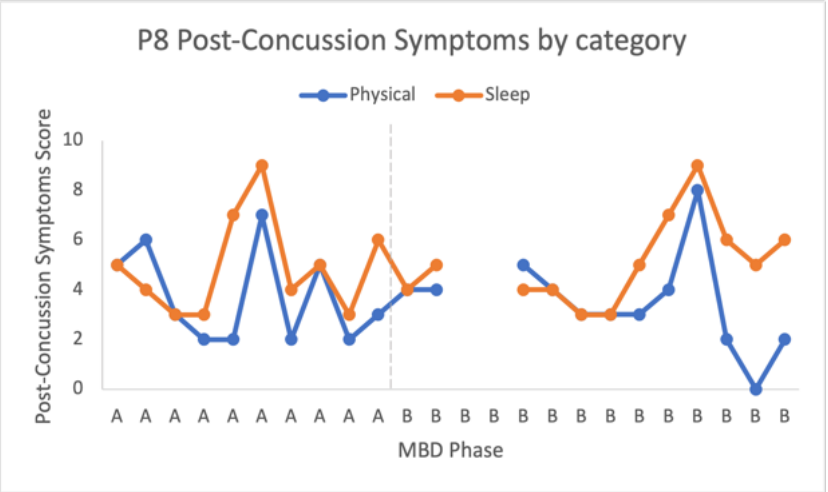


Figure 9a-d. *Participant 8 ANS Measures Across CART*

Figure 9a

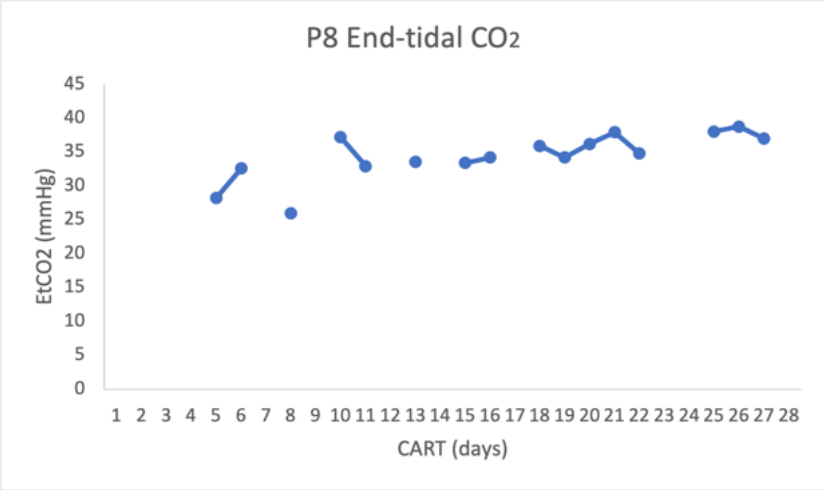


Figure 9b

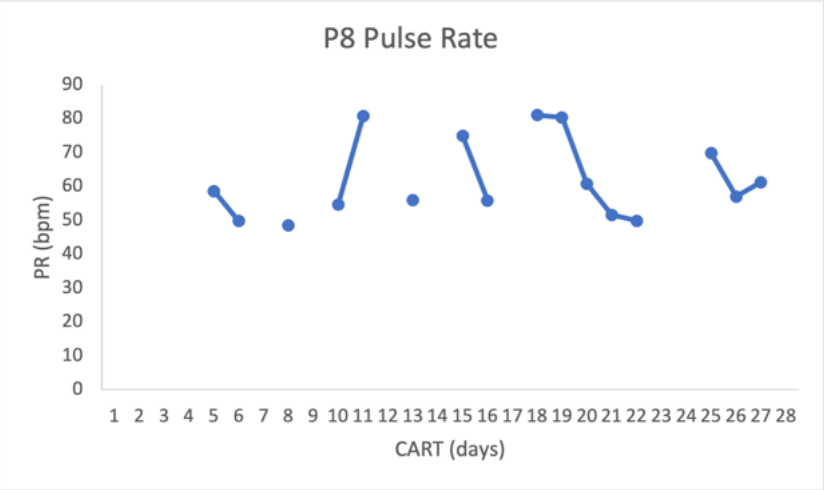


Figure 9c

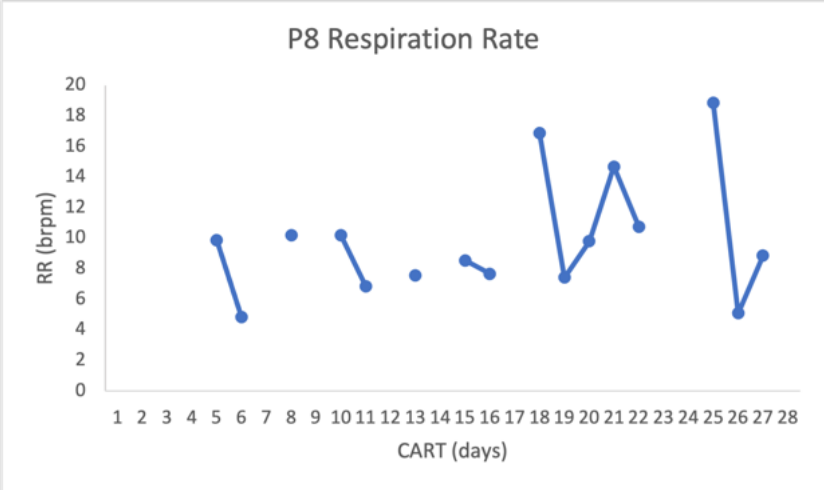


Figure 9d

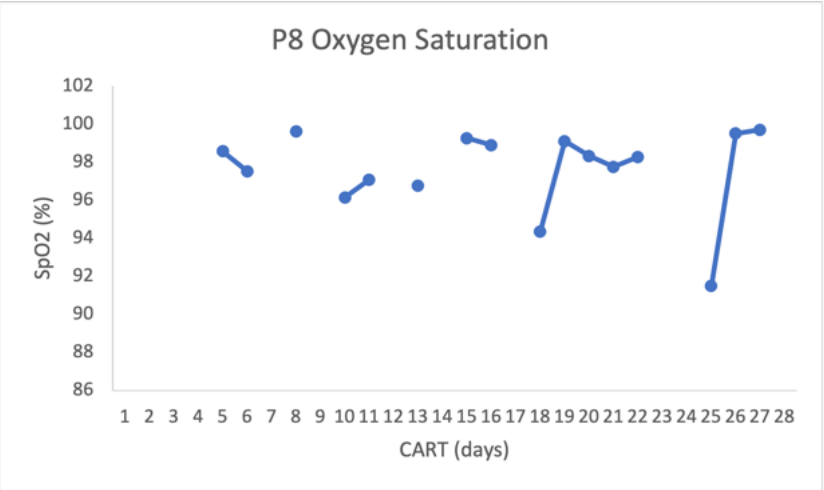


Figure 10a-d. *Participant 9 Daily Measures Scores Across Multiple-baseline Design (MBD) Phase*

Figure 10a

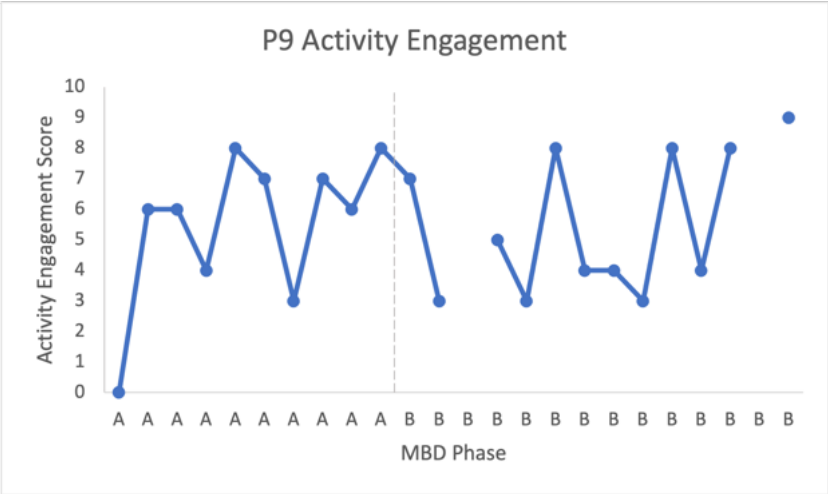


Figure 10b

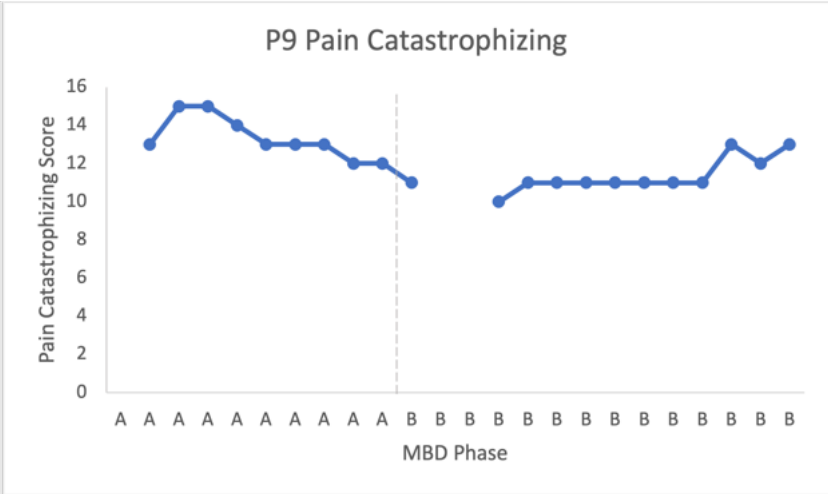


Figure 10c

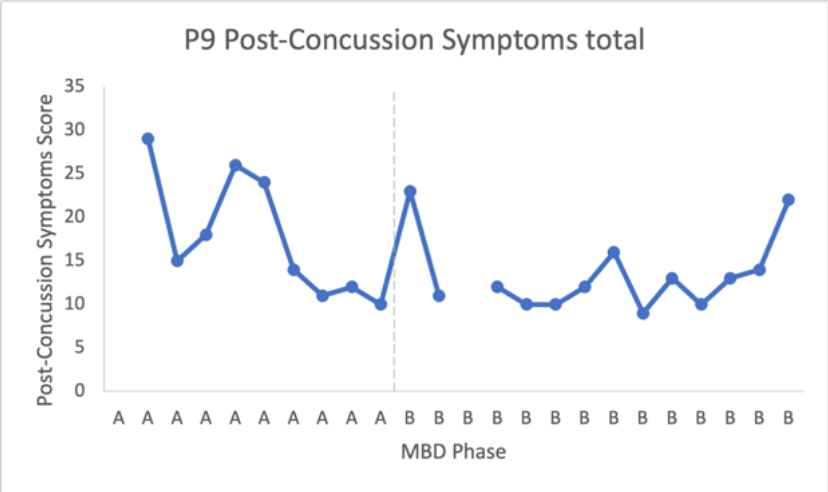


Figure 10d

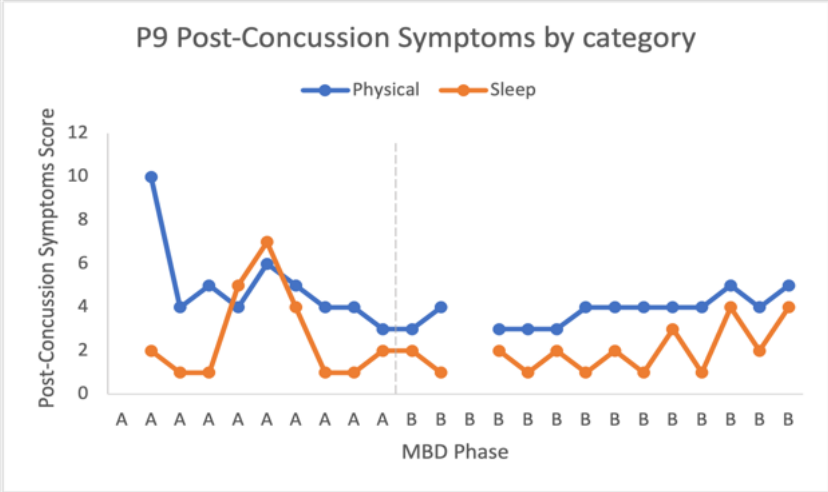


Figure 11a-d. *Participant 9 ANS Measures Across CART*

Figure 11a

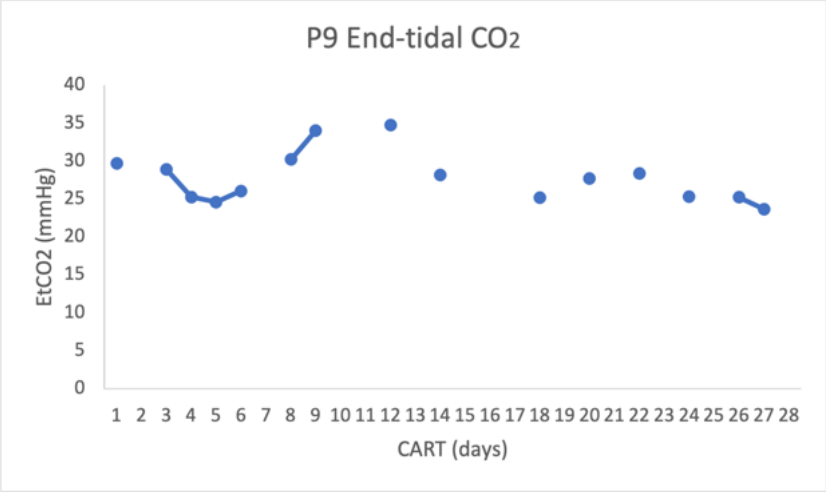


Figure 11b

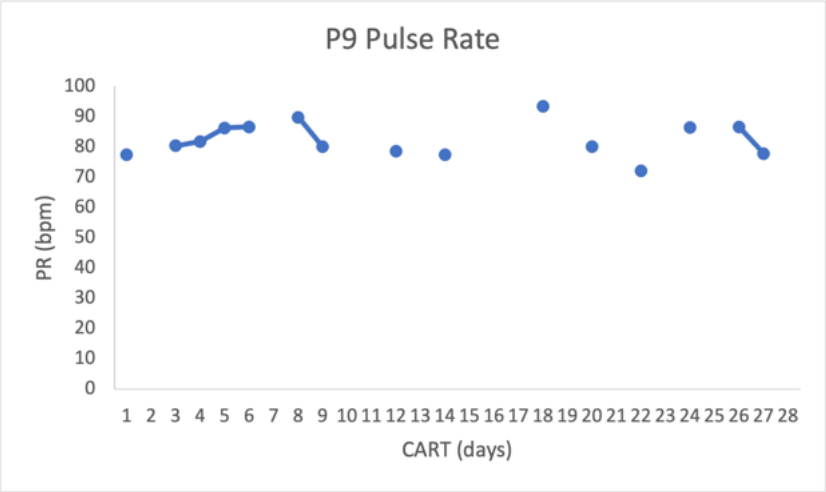


Figure 11c

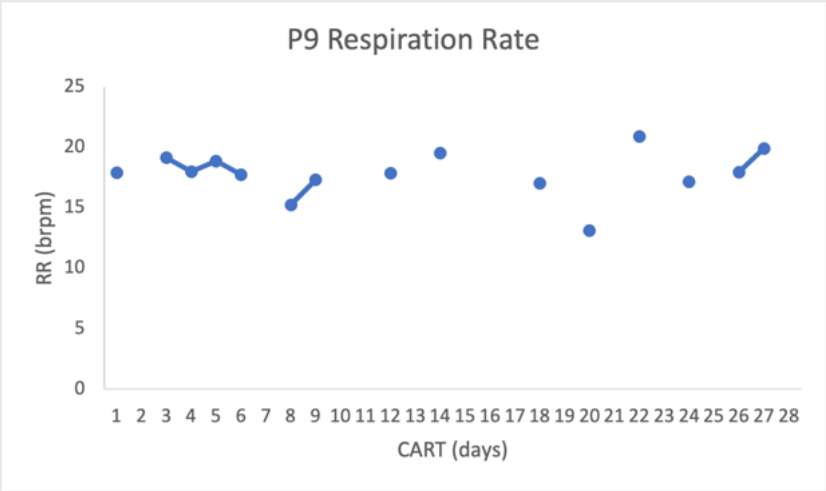


Figure 11d

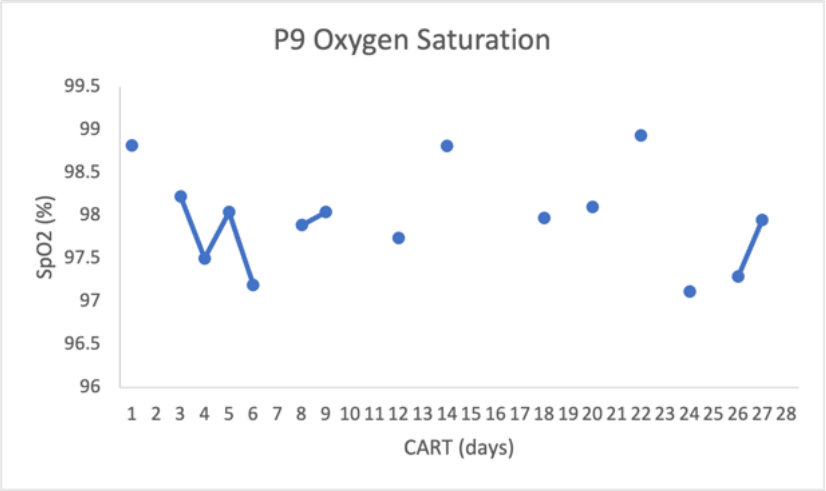


Figure 12a-d. *Participant 1 Daily Measures Scores Across Multiple-baseline Design (MBD) Phase*

Figure 12a

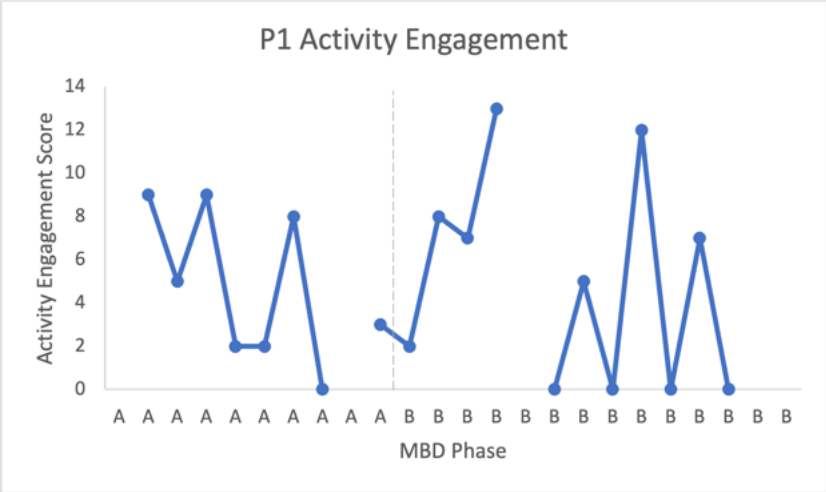


Figure 12b

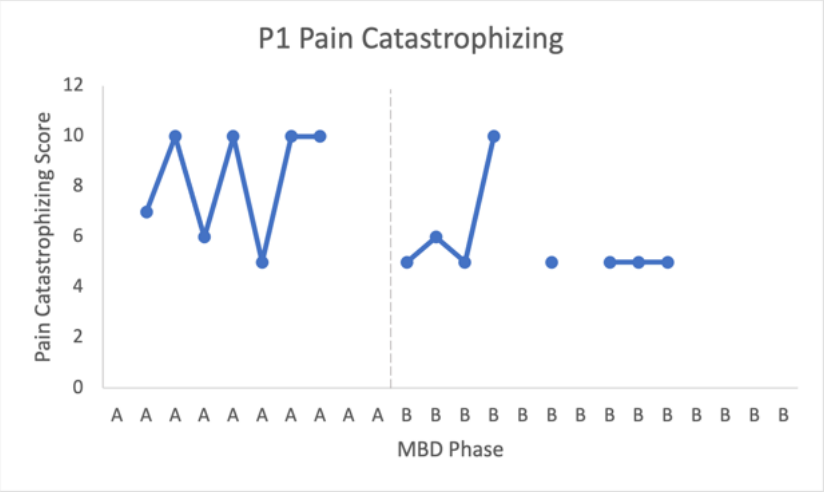


Figure 12c

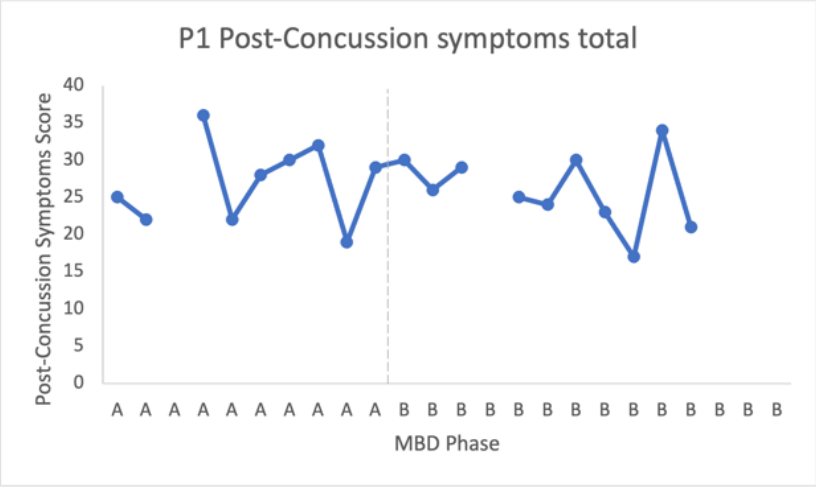


Figure 12d

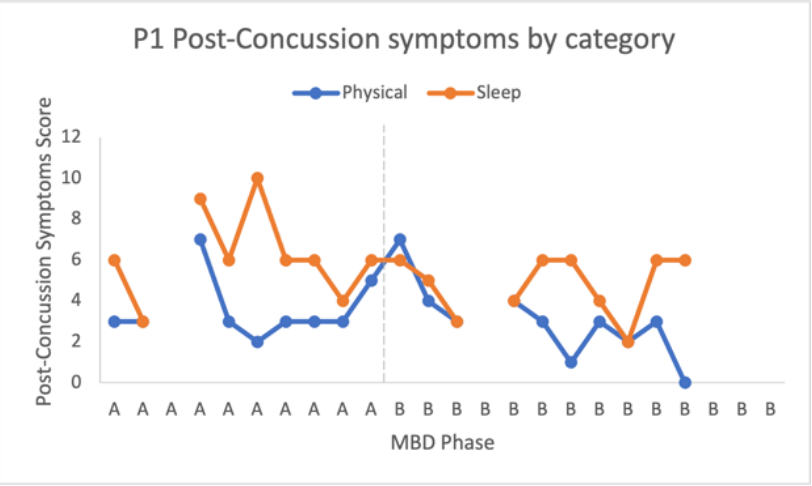


Figure 13a-d. *Participant 1 ANS Measures Across CART*

Figure 13a

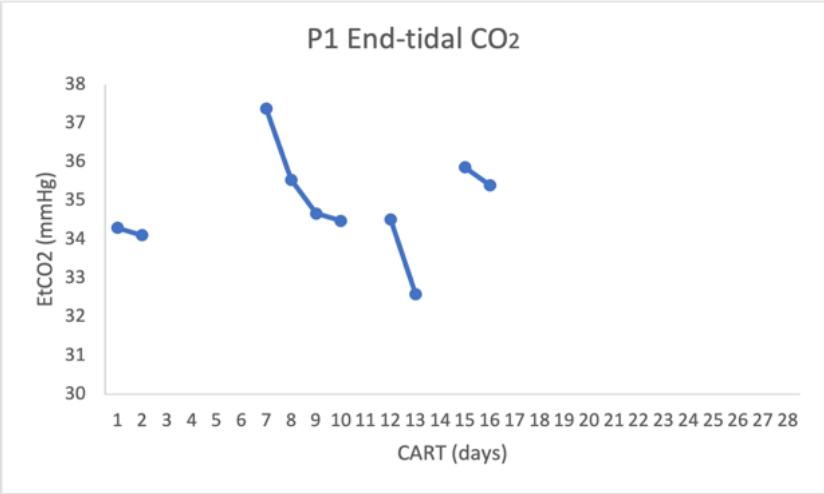


Figure 13b

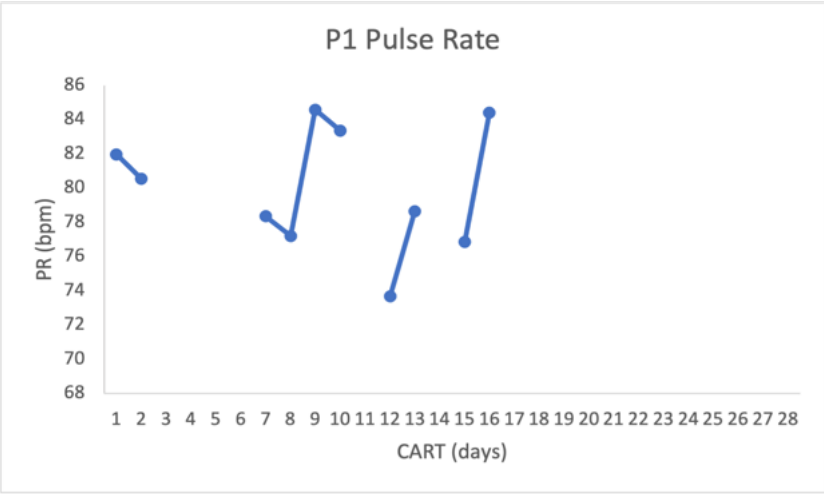


Figure 13c

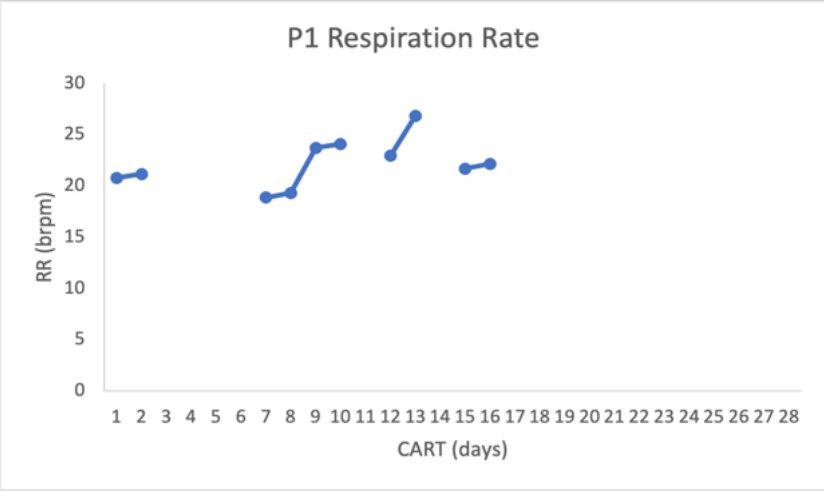


Figure 13d

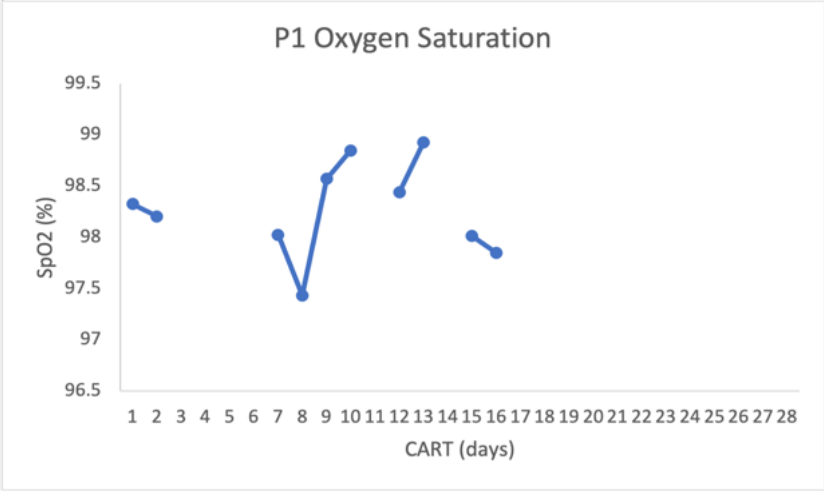


Figure 14a-d. *Participant 2 Daily Measures Scores Across Multiple-baseline Design (MBD) Phase*

Figure 14a

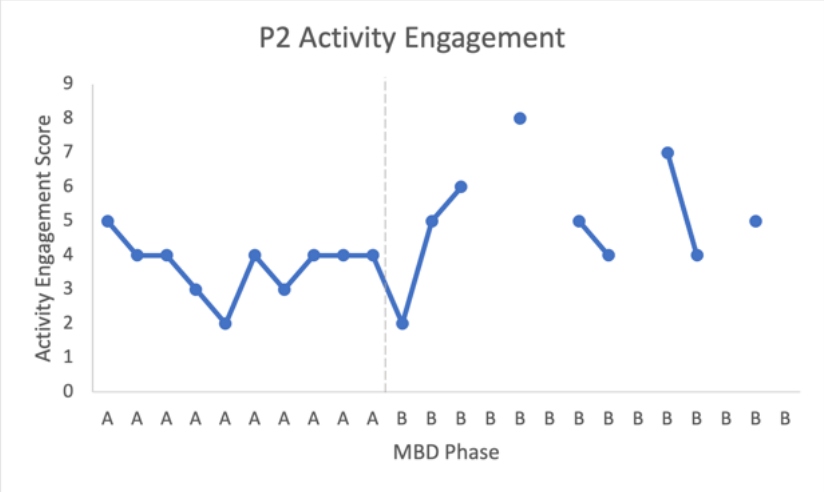


Figure 14b

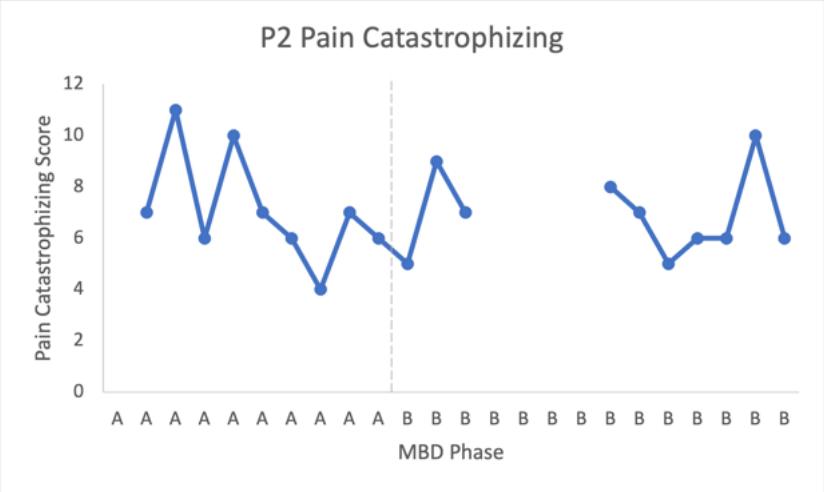


Figure 14c

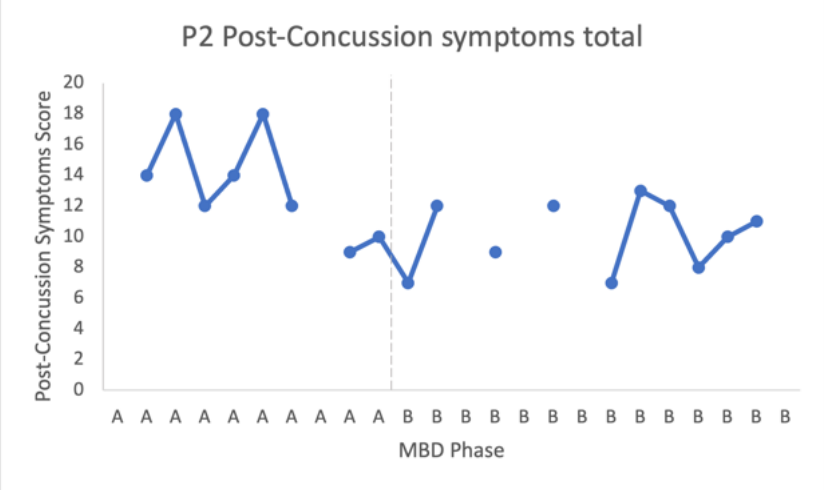


Figure 14d

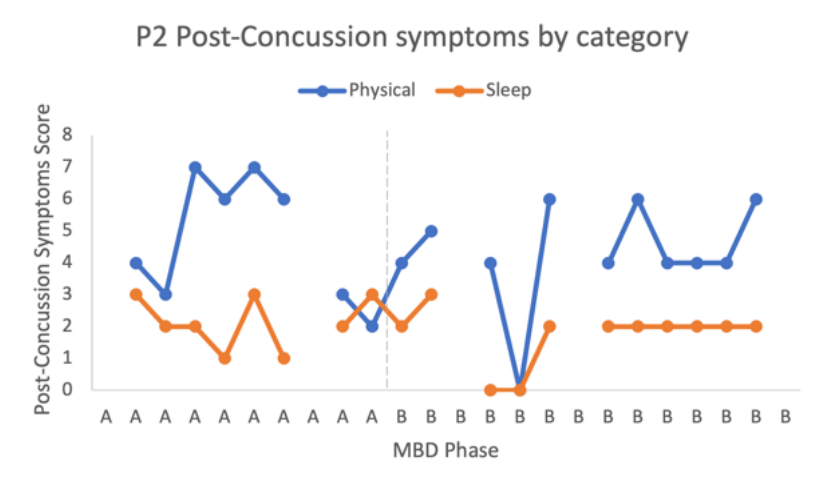


Figure 15a-d. *Participant 4 Daily Measures Scores Across Multiple-baseline Design (MBD) Phase*

Figure 15a

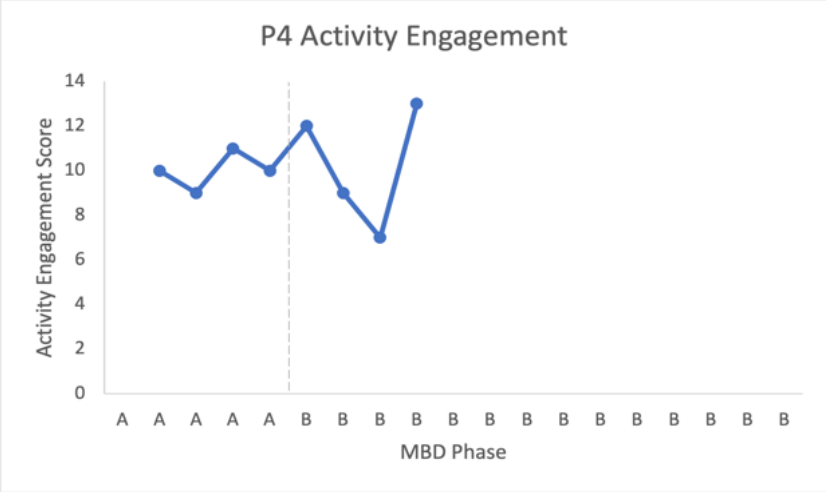


Figure 15b

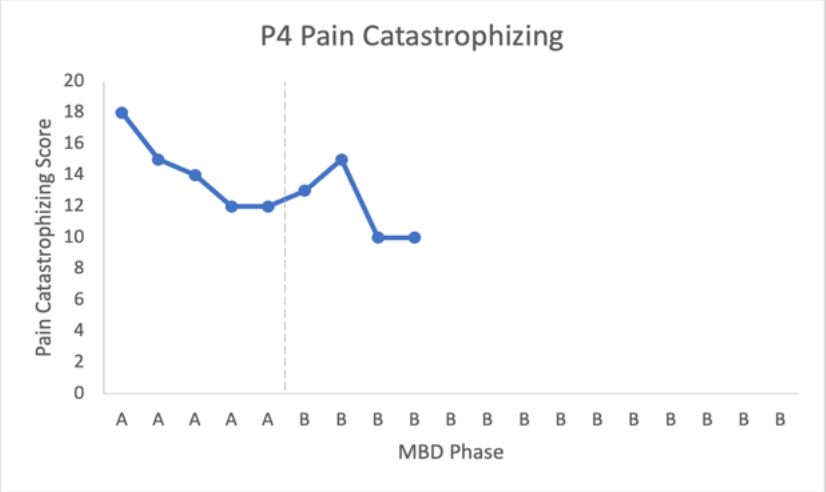


Figure 15c

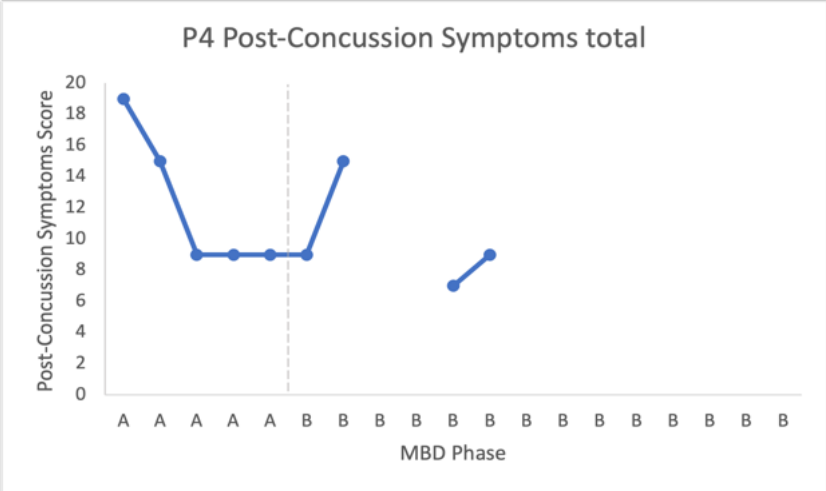


Figure 15d

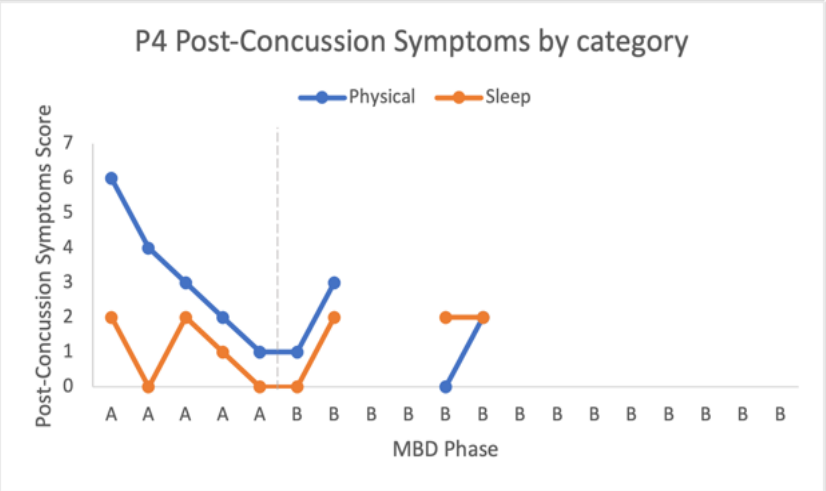


Figure 16a-d. *Participant 5 Daily Measures Scores Across Multiple-baseline Design (MBD) Phase*

Figure 16a

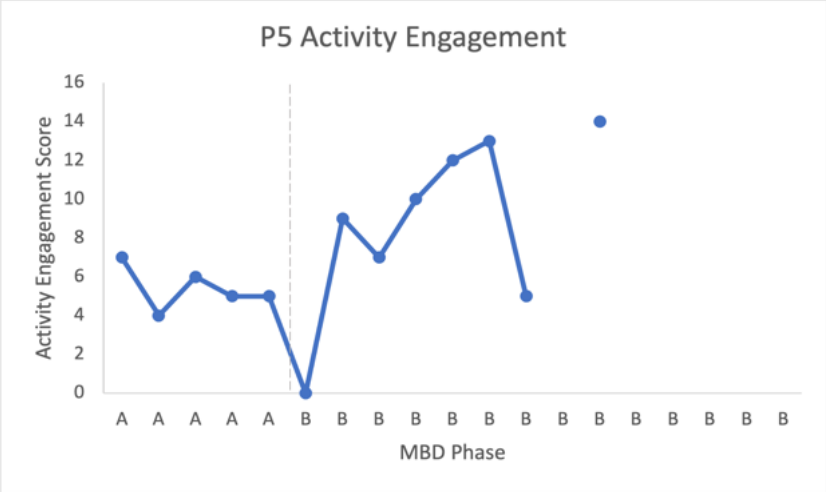


Figure 16b

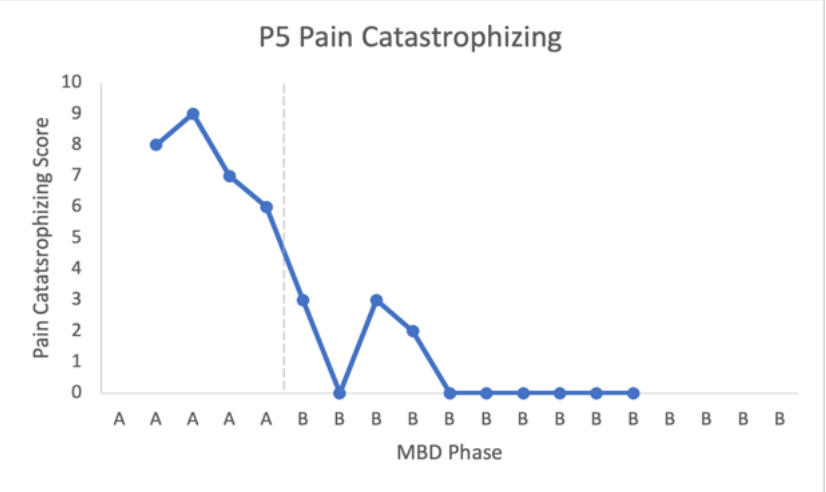


Figure 16c

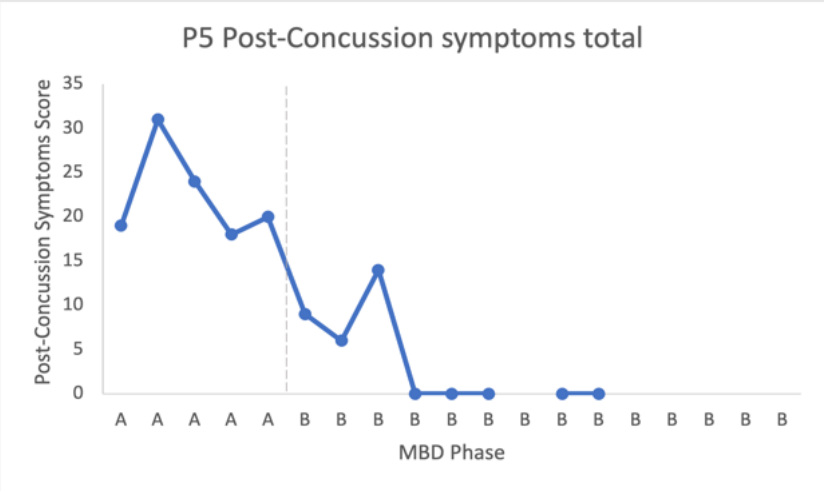


Figure 16d

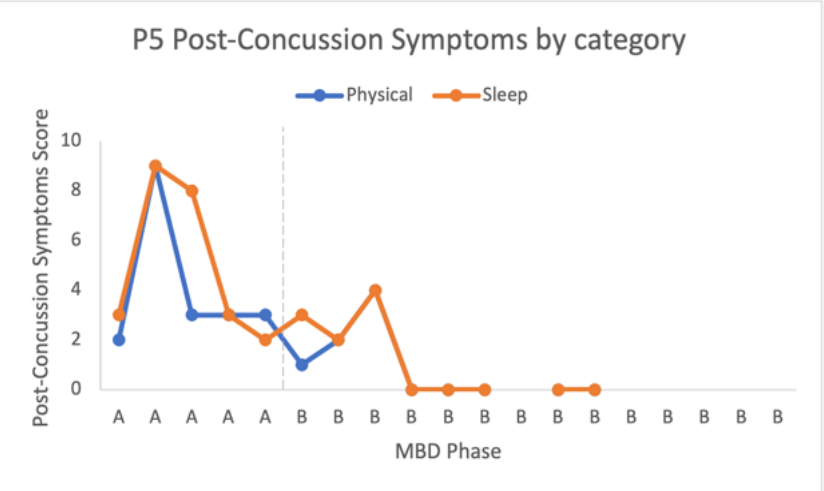


Figure 17. *Significant Main Effect of Treatment Time on Pain Catastrophizing Daily Measure Scores*

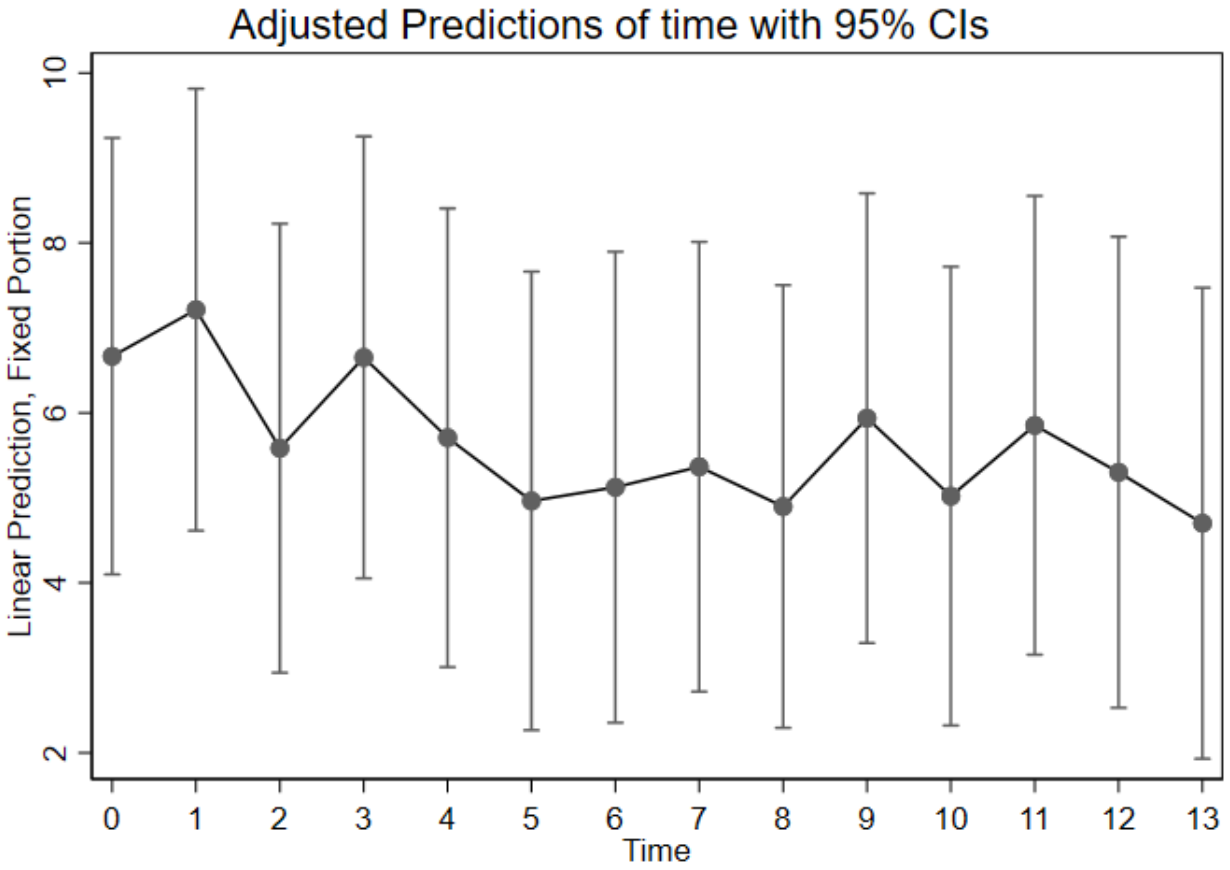


Figure 18. *Significant Main Effect of Treatment Time on Physical Post-Concussion Symptoms Daily Measure Scores*

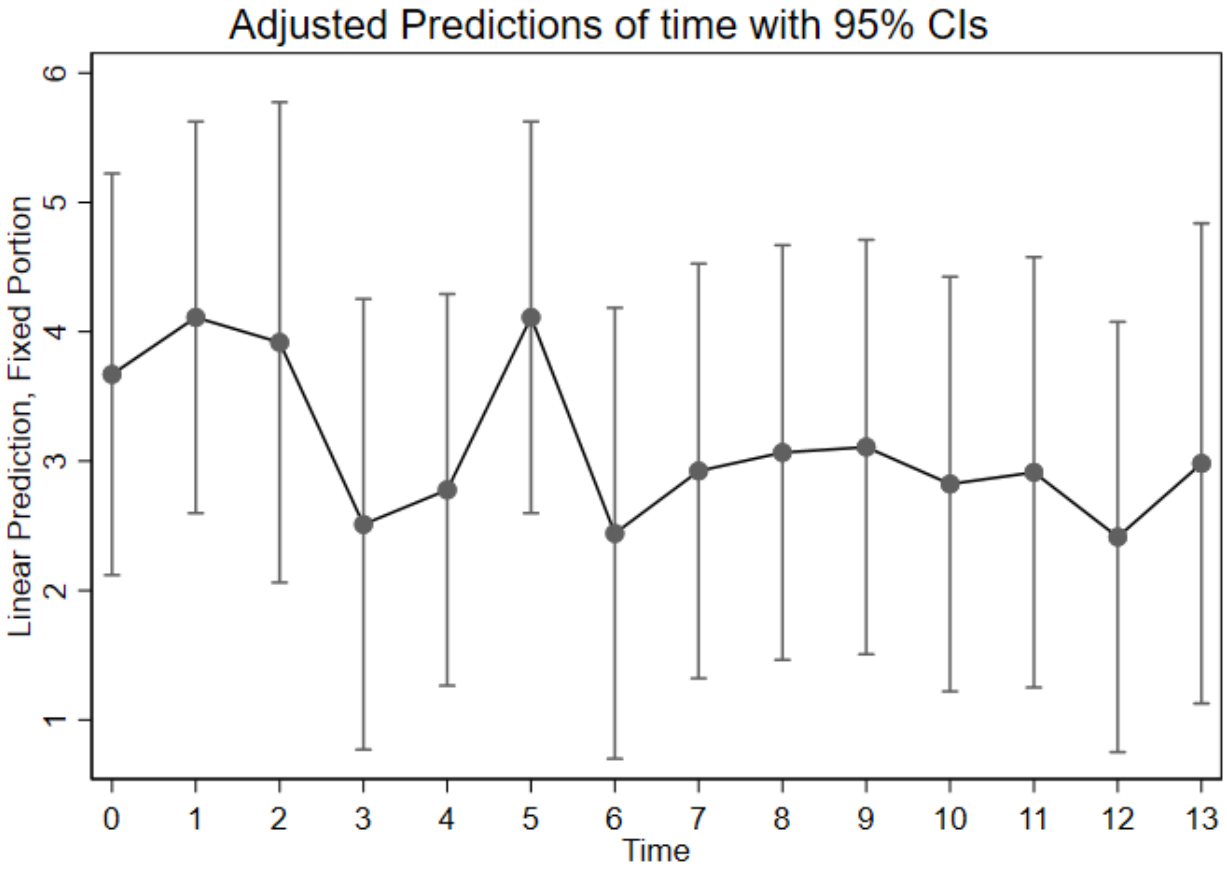
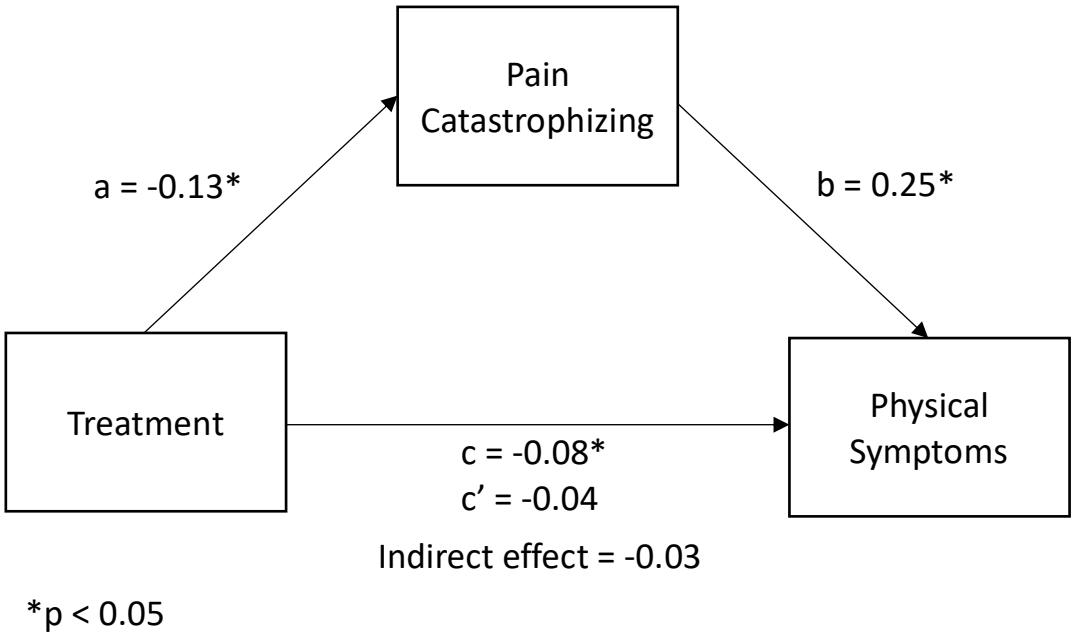


Figure 19. *Mediator Relationship Between Treatment Time and Physical Symptoms*



Appendix A: UCLA Return to Activity Avoidance Inventory

UCLA Return to Activity Avoidance Inventory (RAAvI)

We'd like to know more about how your concussion has affected your ability to do the things you want to do. Some people who have had a concussion may avoid doing different activities because of symptoms (e.g., headaches, dizziness, anxiety, etc.) they experience since the concussion.

List the top three activities that you avoid (e.g., sports, homework, attending class/school, social gatherings). Please be as specific as possible. For example, instead of "sports" you may write "running":

Activity 1: _____

Activity 2: _____

Activity 3: _____

Think about **Activity 1** and answer the following questions:

1. How likely are you to avoid this activity?

None of the time	Some of the time	Half of the time	Most of the time	All of the time

2. How emotionally or physically distressed would you be doing this activity?

None	Mild	Moderate	Strong	Extreme

Now think about **Activity 2** and answer the following questions:

1. How likely are you to avoid this activity?

None of the time	Some of the time	Half of the time	Most of the time	All of the time

2. How emotionally or physically distressed would you be doing this activity?

None	Mild	Moderate	Strong	Extreme

Now think about **Activity 3** and answer the following questions:

1. How likely are you to avoid this activity?

None of the time	Some of the time	Half of the time	Most of the time	All of the time

2. How emotionally or physically distressed would you be doing this activity?

None	Mild	Moderate	Strong	Extreme

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