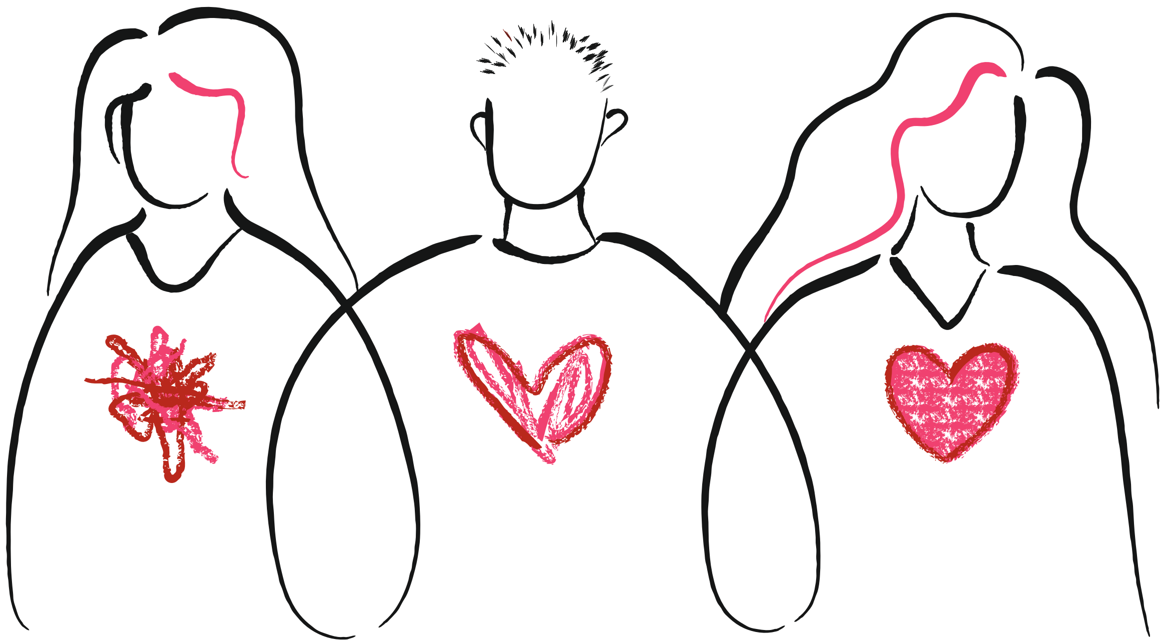
BREATHE AND LET BE

Improving posttraumatic stress and neurobiological dysregulation with game-based meditation therapy among traumatized adolescents in residential care



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Breathe and Let Be

Improving Posttraumatic Stress and Neurobiological Dysregulation with Game-Based Meditation Therapy among Traumatized Adolescents in Residential Care

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COLOPHON

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Chapter 1

GENERAL INTRODUCTION

All studies in this dissertation were conducted in institutions for residential youth care. Youths in these institutions are deemed unable to live at home due to severe psychiatric or behavioral problems, family problems, parental psychiatric problems, or an unsafe home environment—and often a combination of all of these. Although all chapters include a short description of study participants, their clinical characteristics reflect only a small part of the complex stories of the youths that make up this population. Therefore, I would like to introduce *Michaël**, one of our participants.

MICHAËL*

Michaël was four when he was removed from his home by child protection services. His father left the family before Michaël was born. His mother suffered from psychiatric problems and addiction. Michaël and his two-year older sister were neglected and exposed to domestic violence from childhood on.

Child protection services found them at home, alone, underfed, and in dirty clothes. Brother and sister were placed out-of-home in a foster care family. Notably, Michaël had severe temper tantrums. When he threatened someone with a pair of scissors, he was placed with another family. And another. When admitted to residential care, Michaël was placed in a group home with other boys of his age. Yet, he was moved several times again between group homes. It seemed like there was no place where he could fit in.

Michaël longed for nothing more than a place that felt like a home, with care givers that he could count on, and who would not give up on him. With every replacement, Michaël's hope of finding such a place and person diminished even more. And so did his trust in other people. He feels easily threatened, and reacts with aggression. In the interview, I asked Michaël whom he considered to be the most important person in his life. He told me that this was Mickey, the cat of a foster family.

* For privacy reasons, Michaël is not the actual name of the boy.

RESIDENTIAL YOUTH CARE

In the Netherlands, there are approximately 3.5 million children and adolescents under the age of 20 (CBS, 2020). Out of all these youngsters, 12.2% receive some form of youth care. The majority (83.3%) of this 12.2% receive voluntary ambulatory care (Jeugdzorg Nederland, 2018), but there is also a sizeable proportion of youths who receive voluntary residential care (5.3%), or mandatory youth care, in, or outside, their family environment (11.4%). Over 40,000 youths (Jeugdzorg Nederland, 2018) are unable to live at home, mostly due to parental and severe behavioral problems (Knorth et al., 2008). Out-of-home placement includes foster care, as well as open and secure residential care. Foster care consists of placement in a foster family that provides a home-substituting environment. Residential care consists of placement in family homes or institutional group homes. Family homes, like foster care, resemble a home-substituting environment with familial parents and three to six youths (De Baat & Berg-le Clercq, 2013), while youths in residential institutions live in group homes with approximately eight to twelve youths, supervised by trained group care workers who act as professional care givers. Residential institutions include (semi) secure residential youth care [in Dutch: *Jeugdzorg^{Plus}*], open residential youth care, youth psychiatric care, and residential care for youths with intellectual disabilities. At these institutions, youths receive round-the-clock care, (special) education, and treatment to target problem behavior (Knorth et al., 2008).

While the minority of all youths in care are in residential institutions, this still leaves more than 20,000 children and adolescents who live in these institutions (Jeugdzorg Nederland, 2018). Residential care serves youths who need specialized treatment and care. They are unable to live at home or in foster care due to severe, complex behavioral and emotional problems, often combined with psychiatric disorders such as conduct disorder, ADHD, affective or anxiety disorders, and psychotic disorders (Connor et al., 2004). As mentioned above, many youths come from multi-problem families that are characterized by parental alcohol abuse, domestic violence or abuse, and parental arrest (Connor et al., 2004; Smith et al., 2006). Rates of trauma exposure among these youths are staggering. Approximately 85% to 90% of them have already experienced multiple forms of trauma at a young age, such as exposure to domestic violence, physical or emotional neglect, or physical, emotional, or sexual abuse (Briggs et al., 2012; Collin-Vézina et al., 2011). On average, youths report ten abusive events during the course of their lives (Collin-Vézina et al., 2011). Most of the time youths' parents or care givers have been the perpetrators of these traumatic events (Connor et al., 2004), which is extremely harmful, as early caregiving relationships provide the context for the development of children's early models of self-image, attachment patterns, and self-regulation capabilities (Cook et al., 2005).

Unfortunately, among youths in residential care, life stories like Michaël's are the rule rather than the exception. Almost all of them have been exposed to domestic violence, neglect, or abuse, and suffer from a range of negative health outcomes (Collin-Vézina et al., 2011). Prolonged exposure to traumatic stress can lead to the chronic activation and dysregulation of neurobiological stress systems (Bauer et al., 2002; Ellis & Del Giudice, 2019). In Part I of this dissertation, we investigated these neurobiological stress systems in a sample of traumatized youths and in a non-traumatized comparison sample. The past two decades have witnessed an increase in neurobiological research. Methods have evolved and offer new promises. Part II of the dissertation has been designed to evaluate two of these new and innovative methods in neurobiological research. The impact of posttraumatic stress and its negative consequences demand effective treatment. Part III includes three intervention studies: one feasibility study and two randomized controlled trials (RCTs) to evaluate game-based meditation therapy for traumatized youths in residential care.

PART I
TRAUMATIZED YOUTHS' NEUROBIOLOGY

TRAUMA IN YOUTHS IN RESIDENTIAL CARE

When youths repeatedly experience neglect or abuse in their primary caregiving environment, the impact of these traumatic events is twofold. First, there is the reaction to the traumatic event itself, which includes symptoms of posttraumatic stress, such as intrusion, avoidance, hyperarousal, and negative mood and cognitions (American Psychiatric Association, 2013). Second, there is the disruption of youths' emotional, social, cognitive, and behavioral development, resulting in disturbances of affective and interpersonal self-regulation capacity (Cloitre et al., 2009; Cook et al., 2005; Van Der Kolk, 2005).

Exposure to trauma increases the risk of psychological and behavioral problems (e.g., anxiety, depression, and aggression; Briggs et al., 2012; Collin-Vézina et al., 2011b; Maniglio, 2013, 2015); substance use (Briggs et al., 2012); sexual risk behavior and victimization (Arata, 2006; Collin-Vézina et al., 2011b; Smith et al., 2006); delinquency (Ford et al., 2012; Hodgdon et al., 2018; Smith et al., 2006); self-harm and suicidality (Briggs et al., 2012); and teenage parenthood, parenting problems, and adverse intergenerational effects resulting in offspring problems (Roberts et al., 2004). Trauma also has negative effects on physical health (Afari et al., 2014) and dysregulates neurobiological stress response systems (Bauer et al., 2002; Bremner & Vermetten, 2001; Corrigan et al., 2011; De Bellis, 2001; Ellis & Del Giudice, 2019; Gunnar et al., 2006; Perry, 2009). These adverse effects are more severe and pervasive as the severity of traumatization increases: more traumatic events and more severe traumatic experiences are associated with the most adverse outcomes (Cicchetti et al., 2001a; Collin-Vézina et al., 2011; Ouellet-Morin et al., 2019).

THE NEUROBIOLOGY OF TRAUMATIC STRESS

In the face of exposure to stress, our body's stress systems get activated. Chronic physiological activation due to prolonged exposure to traumatic stress can seriously disrupt neurobiological stress systems. In healthy individuals, these stress systems generate an adaptive response in the face of threat. Stressors activate the autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal (HPA) axis systems. The ANS consists of two reciprocally coupled systems: the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). The SNS prepares the body for immediate action (i.e., the 'fight-or-flight' response) through its activation. This results in a rapid increase of cardiac output. When the stressor disappears, the PNS inhibits sympathetic activation and facilitates bodily homeostasis (i.e., recovery and digestion) (Berntson et al., 2008). An adaptive stress response increases SNS activity and decreases PNS activity, and vice versa for adaptive recovery, illustrating the reciprocal coupling (Berntson et al., 1991). Whereas physiological changes due to SNS activation only take seconds, HPA activation has a slower onset and longer duration. HPA axis activation results in the production of steroid hormones and is typically assessed by measuring its final product, cortisol (Bauer et al., 2002).

Over the last decades, research has shown that neurobiological development is shaped by an individual's experiences. Repeated and prolonged stress can lead to maladaptive alterations of both the ANS and HPA axis that last for long after the original stressor has disappeared (Bauer et al., 2002; Ellis & Del Giudice, 2019; Gunnar et al., 2006; Van der Kolk, 2005). For many youths in residential care, their traumatic past has shaped their neural systems, which are involved in stress reactivity. Notably, this dysregulation of youths' neurobiological stress systems has been proposed as a key mechanism in the development and maintenance of psychological and behavioral problems after trauma (Bauer et al., 2002; Ellis & Del Giudice, 2019; Gunnar et al., 2006).

The experience of traumatic events leads to attentional hypervigilance for threat (Dalgleish et al., 2001) and can result in both over- and under-reactivity to stimuli. While healthy individuals are able to integrate cognitive and emotional processing, traumatized youths can be highly responsive and emotionally flooded, or non-responsive and emotionally detached. Both states do not include adequate cognitive thinking (Corrigan et al., 2011). Over-reactivity is referred to as hyperarousal and includes strong SNS-dominated physiological reactivity. This is the 'fight-or-flight response' that prepares the body for mobilization, and to either fight or flee from the threat (Porges, 2007). Even mildly stressful stimuli are considered threatening, which often leads to misinterpretation of other people's intentions, and thus to persistent affective and interpersonal problems (Van der Kolk, 2014). The opposite of over-reactivity or hyperarousal is under-reactivity, which includes blunted emotional and physiological responses to stimuli, and it is referred to as hypoarousal. This is a submissive PNS-dominated response characterized by flat affect, numbing, collapse, and dissociation (Corrigan et al., 2011).

Knowledge of the neurobiological correlates of trauma may enhance treatment specificity and effectiveness. Traumatized youths compose a complex, heterogenous group that can differ in age, gender, type, and length of traumatic experiences, as well as in their level of physiological stress reactivity. This heterogeneity impedes both trauma assessment and treatment. Both PNS and HPA axis parameters can predict treatment effectiveness in youths (Lipschutz et al., 2017; Van De Wiel et al., 2004). While much research has been devoted to understanding the neurobiological stress systems in relation to trauma, most studies have examined either the ANS or the HPA axis. Additionally, when evaluating the ANS, many studies include PNS effects only. Yet, if evaluated in isolation, interactional effects between different systems can obscure true effects (Bauer et al., 2002). Therefore, in the current dissertation we investigated both SNS and PNS parameters in conjunction with HPA axis activity.

PART II
NEUROBIOLOGICAL RESEARCH METHODOLOGY

METHODOLOGICAL ISSUES IN NEUROBIOLOGICAL RESEARCH

In research on the ANS, cardiovascular parameters, such as heart rate variability (HRV), are usually measured with electrocardiography (ECG). The VU University Ambulatory Monitoring System (VU-AMS; Vrije Universiteit, Amsterdam, the Netherlands) is considered a gold standard ECG device with proved validity (De Geus et al., 1995; Willemsen et al., 1996). Although the VU-AMS provides an excellent opportunity for ambulatory measurements in real-life contexts, the device is expensive, analysis is time-consuming, and both sensor application and analysis requires a well-trained professional. For operation, five electrodes are placed on the back and two on the chest. Participants need to partially undress and lift up their shirt for placement of the electrodes. In a high-risk and vulnerable population such as youths in residential care, this can lead to feelings of tension and insecurity, in particular among those with a history of sexual abuse. Simpler and less invasive monitoring systems such as wearable wristbands have been developed as a more convenient way to measure physiological parameters. Although the reliability and validity of the VU-AMS in obtaining HR parameters has been established (De Geus et al., 1995; Willemsen et al., 1996), there is still debate on the validity of wearables as HR monitoring systems.

Until the last decade, HPA axis activity could only be assessed with cortisol level analysis in blood serum, urine, or saliva. However, blood and urine analysis call for invasive sampling techniques, and while saliva samples are relatively easy to obtain, salivary cortisol levels are subject to major intra- and interindividual fluctuations and circadian, ultradian, and infradian rhythms (van Ockenburg et al., 2015). Thus, while salivary sampling provides an excellent opportunity to capture acute cortisol levels and cortisol reactivity, its major fluctuations impede the assessment of cortisol levels over a longer period of time. These shortcomings have led to the development of a new method to measure average long-term cortisol levels: the extraction of cortisol from hair. Cortisol levels in hair provide a reliable way to measure chronic stress exposure, and also present the opportunity for retrospective analysis. As hair grows at approximately one centimeter per month, different segments of hair can be compared to assess the change in cortisol over time (Staufenbiel et al., 2013). Although hair cortisol measurements have been used previously to assess the relationship between cortisol and traumatic experiences in youth (Simmons et al., 2016; Straub et al., 2017), these studies mainly included community participants who had experienced non-intentional trauma, such as an accident. Straub and colleagues (2017) included a subsample of participants with clinical problems who experienced neglect and abuse, but this only consisted of 22 participants.

PART III
TREATMENT FOR TRAUMATIZED YOUTHS

TRAUMA TREATMENT

Up to this point, characteristics of residential care and traumatized youths in residential care, the neurobiology of stress, and neurobiological measurement methods have been discussed. Given the pervasiveness and far-reaching negative consequences of trauma, there is a great need for effective treatment. Posttraumatic symptoms that persist for more than six months after the traumatic situation has come to an end are unlikely to disappear without appropriate treatment (Hiller et al., 2016). Yet, although most youths in residential care have been exposed to traumatic events, their traumas often go unrecognized and untreated. This is due to inadequate trauma assessment, the youths' lack of motivation for treatment, and clinicians who fear that youths cannot cope with the intensity of trauma treatment.

Residential care lacks consistent, adequate trauma assessment at intake (Ai et al., 2013; Milne & Collin-Vézina, 2015). Youths are primarily admitted to residential care due to externalizing behavior such as aggression (Connor et al., 2004). Most treatment approaches target their externalizing problems (De Swart et al., 2012) and tend to neglect the fact that trauma exacerbates aggressive behavior (Ford et al., 2012; Maniglio, 2015). Thus, for many youths in residential care, their behavioral symptoms are targeted in therapy, while the underlying cause of their aggressive behavior – their trauma – remains untreated. This may make some of their posttraumatic symptoms vanish, while others still go unnoticed, untreated, and interfere with their development. Fortunately, over recent years there has been increasing attention to the development and implementation of more trauma-informed approaches (Lieberman, 2014).

Engaging youths is one of the most challenging tasks faced by clinicians (Crenshaw, 2008), particularly those in residential care (Van Binsbergen, 2003). Traumatized youths tend to have a general distrust of others due to disorganized attachment patterns (Cook et al., 2005), which impede the development of a therapeutic relationship and treatment progress (Cohen et al., 2012; Green & Myrick, 2014). Particularly in residential care, youths have had a substantial number of prior placements and replacements with concomitant treatment that were not effective for them (Connor et al., 2004). This makes them doubt the value of treatment and decreases their motivation for future treatment approaches (Greenwald, 2006). However, without appropriate treatment, posttraumatic symptoms are likely to continue over time (Hiller et al., 2016).

Another reason why traumatized youths often do not receive treatment is related to the characteristics of trauma treatment. The most widely used forms of treatment are trauma-focused cognitive behavioral therapy (TF-CBT) (Cohen et al., 2012) and eye movement desensitization and reprocessing (EMDR) (Shapiro, 1989). These treatments are effective among children and adolescents (Leenarts et al., 2013; Silverman et al., 2008; Stallard, 2006; Wethington et al., 2008), but TF-CBT tends to be mainly cognitively oriented and relies on verbal expression. Both include exposure techniques that can trigger strong emotions (Warner et al., 2013). Yet, as trauma affects youths' capacity to control and regulate their impulses and emotions (Cook et al., 2005), they are often unable to sufficiently connect with their emotions and express their internal processes, and they cannot tolerate their physiological responses during trauma processing. In such a state of dysregulation, one's capacity for cognitive processing and working memory, which is required for treatment to succeed in promoting change, is not available (Corrigan et al., 2011; Lanktree & Briere, 2008; Warner et al., 2013). However, many traditional forms of trauma treatment are mainly targeted at problems in cognitive and relational domains (Cohen et al., 2012; Warner et al., 2013), while these problems may originate in dysregulation of sensory integration and self-regulatory capacities. To be most effective, trauma treatment would first need to address and improve the baseline capacity to regulate one's emotions and physiological responses before focusing on cognition and relations. There is indeed a growing body of research that supports the shift from mainly cognitive oriented and verbally dependent therapies to interventions that target physiological sensations and stress regulation abilities (Van der Kolk, 2014; Warner et al., 2013).

BODY-FOCUSED TREATMENT: MINDFULNESS, MEDITATION & YOGA

Interventions that target physiological sensations and stress-regulation abilities, called body-focused interventions, include – but are not limited to – mindfulness, meditation, and yoga. Although there are subtle differences between these three, these forms of treatment have elements in common. The terms mindfulness and meditation are often used in similar contexts, but these are not interchangeable. Mindfulness is not just formal practice, but more like a state of being. It includes intentional shifting of non-judgemental attention to the present moment. It can include meditation and yoga, but there are many more ways to practice mindfulness (Kabat-Zinn, 1994). Meditation involves the formal practice of focusing on a repetitive object such as one's breath, or repeating a word or phrase to bring about a state of reduced physiological arousal without thoughts interfering. Meditation practice can increase one's capacity to control automatic reactions and help allocate attention more productively (Lang et al., 2012). Yoga consists of breathing, postures, and meditation (Van der Kolk, 2014). Yoga breathing can have physical effects similar to meditation, as both activate the parasympathetic nervous system and induce altered states of consciousness (Brown & Gerbarg, 2009). Yoga posture practice focuses on physical sensations, which lead to increased awareness of physical elements that are related to emotions, such as body tension, a rapid heartbeat, and short, shallow breaths (Van Der Kolk et al., 2014). These forms of patterned, repetitive intervention can target problems that originate from dysregulated sensory integration and the regulation of emotional and physiological impulses, that are assumed to underlie posttraumatic symptoms in the cognitive and relational domains (Perry, 2009).

One particularly promising approach in the treatment of traumatized youths is fostered by meditation techniques and deep-breathing practices that emphasize one's bodily sensations and increase a sense of control over the body. This reduces feelings of stress, and improves both emotion-regulation and cardiovascular activity (Sarang & Telles, 2006; Streeter et al., 2012; Wu & Lo, 2008). Meditation-based approaches are also thought to address emotional under- and overregulation, which are both core features of posttraumatic stress (e.g., hyperarousal or emotional numbing) (Boyd et al., 2018). Studies on physiological outcomes have shown that meditation can restore activity and connectivity in brain regions associated with posttraumatic symptoms (Boyd et al., 2018), can lead to more balanced patterns of neurobiological stress responses (Pascoe et al., 2017), and can modulate both HPA axis and ANS reactivity (Nguyen-Feng et al., 2019). Moreover, the formal practice setting of meditation makes it relatively easy to include in treatment. It does not require physical expression so it can be practiced by everyone and everywhere. Research to date on the effectiveness of meditation interventions for posttraumatic stress indeed shows encouraging findings among adolescents (Spinazzola et al., 2011a) and adults (Boyd et al., 2018; Kim et al., 2013; Macy et al., 2018; Nguyen-Feng et al., 2019; Pascoe et al., 2017).

Therefore, in this dissertation, we aimed to investigate the potential of meditation therapy for traumatized youths in residential care.

A NOVEL APPROACH IN YOUTH TREATMENT: GAME-BASED INTERVENTIONS

Another basic design decision regarding the intervention that we aimed to test was related to its delivery model. Specifically, we intended to engage youths in treatment with a game-based intervention. Over the last decade, there has been a rapid growth of technology, and many studies indicate the potential that 'serious games' have to improve upon the effectiveness, efficiency, reach, costs, and appeal in the context of mental health care (Lau et al., 2017). Game-based interventions are a novel strategy to engage youths in treatment, by making use of their intrinsic motivation to play games (Granic et al., 2014). The potential that games have for being appealing and engaging for youths is reflected by their popularity: almost all youths worldwide play games on a daily basis (Lenhart et al., 2008). This holds great promise for youth treatment in general, and in particular for youths in residential care, who are often not motivated for treatment (Van Binsbergen, 2003). Previous studies that evaluated game-based interventions among adolescents in residential care not only reported effective outcomes, but also high user satisfaction and low attrition (Kahn et al., 2009, 2013; Schuurmans et al., 2015, 2018). These are promising results, since adolescents in residential care usually lack the motivation to change their behavior (Van Binsbergen, 2003), when motivation is a key predictor of treatment effectiveness (Harder et al., 2012).

Yet, the advantages of game-based interventions over traditional forms of treatment extend further than their potential for engagement. There are other limitations that are inherent in the didactic delivery models of cognitive-oriented treatments, such as TF-CBT. These rely largely upon imparting psychoeducational information (Weisz & Kazdin, 2010), which not only lacks intrinsically motivating elements, but also offer knowledge with limited opportunity for practice. While many treatment programs incorporate exercises such as role-playing (Weisz & Kazdin, 2010), these rarely manage to provoke genuine emotions akin to those that arise during real-world conflicts. Often, youths may *know* very well about acceptable behavior, but they do not *act* upon that knowledge in emotionally challenging situations. This leaves a gap between knowledge and behavior, resulting in the limited generalizability of treatment effects to real life (Weisz & Kazdin, 2010). Game-based learning includes *less thinking* and *more doing*, which suits youths better than memorizing information (Vygotsky, 1978), particularly in the case of those with an intellectual disability (Evmenova & Behrmann, 2011). Furthermore, gameplay is characterized by its repetitive nature, which promotes long-term learning (Rosas et al., 2003). The in-game environment offers adolescents the opportunity to practice with acquired techniques and strategies until these are automatized and can ideally be generalized to contexts outside therapy (Granic et al., 2014).

THE PRESENT DISSERTATION

The aim of the current dissertation is three-fold. First, we aimed to provide insight with regard to the alterations of traumatized youths' neurobiological stress systems (PART I). We investigated sympathetic, parasympathetic, and HPA axis parameters among traumatized adolescents in residential care and a non-traumatized comparison sample. Both basal activity during rest and reactivity to acute social stress were evaluated. The outcomes of this study are described in **Chapter 2**.

The second aim of this thesis was to address methodological issues in neurobiological research in two ways: (1) by evaluating the validity of a wearable wristband to assess autonomic nervous system parameters, and (2) by making use of a new method to assess long-term cortisol exposure that has been validated, but not previously used in a clinical population of traumatized adolescents in residential care. We aimed to evaluate the accuracy and predictive value of a wearable wristband to measure heart rate variability parameters in traumatized adolescents. While devices such as the VU-AMS are a valid way to monitor physiology, sensor application to the chest and back can be invasive for vulnerable, clinical populations. Simpler and less invasive monitoring systems, such as wearable wristbands, yield high expectations but are not extensively validated. **Chapter 3** describes a comparison of the Empatica E4 wristband and the VU-AMS as a gold standard reference. Two studies in this dissertation included outcomes on hair cortisol in traumatized adolescents. In these studies, we assessed hair cortisol levels as a measure of long-term cortisol exposure. The outcomes on hair cortisol are included in **Chapter 2** and **Chapter 7.**

Our third and final aim was to rigorously test game-based meditation therapy as an intervention for traumatized youths in residential care. We started by conducting a feasibility study that evaluated three game-based meditations interventions that incorporated either bio- or neurofeedback. We assessed the potential of these interventions to teach youths how to successfully regulate their physiological stress, user satisfaction, as well as the interventions' preliminary effects on posttraumatic symptoms, stress, anxiety, and aggression. **Chapter 4** presents the results of this study. The intervention that was positively evaluated in all outcomes was *Muse*. The feasibility study extended to an RCT on the effectiveness of *Muse* compared with treatment as usual (TAU). **Chapter 6** describes the main outcomes of this RCT, including effects on posttraumatic symptoms and stress (primary outcomes), as well as on anxiety, depression, and aggression (secondary outcomes). As a next step, we investigated the potential of *Muse* to normalize alterations of neurobiological stress systems after trauma. Outcome effects on SNS, PNS, and HPA axis parameters that were measured during rest and while performing a social stress task (all secondary outcomes) are described in **Chapter 7**.

Lastly, **Chapter 8** presents a summary and general discussion of the main findings of these studies. Following these discussions, limitations, clinical implications, and directions for future research on trauma and neurobiology, wearable recording devices, and game-based meditation interventions are examined.

1

Chapter 2

Alterations of autonomic nervous system and HPA axis basal activity and reactivity to stress: A comparison of traumatized adolescents and healthy controls

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ABSTRACT

Alterations in neurobiological stress systems such as the autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal (HPA) axis contribute to the development and maintenance of psychological and behavioral problems after traumatic experiences. Investigating neurobiological parameters and how these relate to each other may provide insight into the complex mechanisms at play. Whereas the preponderance of studies focuses on either the ANS or the HPA axis separately, the current study is the first to evaluate relations between posttraumatic stress and both basal activity during rest and stress reactivity of the ANS as well as the HPA axis in a sample of traumatized adolescents and healthy controls.

The traumatized sample (n = 77), based on clinical levels of posttraumatic stress, was a convenience sample that was recruited within residential institutions, was compared to a healthy control sample (n = 48) recruited within the general community. For the ANS, we expected increased SNS and decreased PNS activity during rest and increased SNS and decreased PNS reactivity to social stress among traumatized adolescents compared to healthy controls. Regarding the HPA axis, we expected increased basal cortisol levels and decreased cortisol reactivity to stress in the traumatized sample.

Compared to healthy controls, traumatized adolescents exhibited significantly higher sympathetic and lower parasympathetic activation during rest and increased sympathetic reactivity to acute stress (ANS parameters). Outcomes on the HPA axis (i.e., cortisol) indicated that traumatized adolescents showed increased cortisol levels during rest and blunted cortisol reactivity to acute stress.

Implications for clinical relevance and trauma-focused treatment purposes are discussed.

INTRODUCTION

The majority of adolescents in residential care have been exposed to domestic violence, neglect, and emotional, physical, or sexual abuse (Collin-Vézina et al., 2011). These traumatic experiences influence the neural systems that are involved in stress reactivity. Repeated and prolonged activation of these systems can lead to maladaptive alterations that last for long after the original stressor has disappeared. The dysregulation of adolescents' neurobiological stress systems has been proposed as a key mechanism in the development and maintenance of psychological and behavioral problems after trauma (Bauer et al., 2002; Ellis & Del Giudice, 2019). In healthy individuals, neurobiological stress systems generate an adaptive response in the face of threat. Stressors activate the autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal (HPA) axis systems. The ANS prepares the body for immediate action (i.e., the "fight-or-flight" response) through activation of the sympathetic nervous system (SNS). This results in a rapid increase of cardiac output. When the stressor disappears, the parasympathetic nervous system (PNS) inhibits sympathetic activation and facilitates bodily homeostasis (i.e., recovery and digestion). SNS and PNS activity can be assessed by pre-ejection period (PEP) and respiratory sinus arrhythmia (RSA), respectively. PEP reflects the time interval between the beginning of electrical ventricle stimulation and cardiac ejection (Berntson et al., 2008). SNS activation decreases PEP and shorter PEP intervals correspond to increased heart rate (HR). RSA is a marker of PNS influences on HR and reflects a coupling of HR and respiration which results in systematic variability in HR during inhalation (Thayer et al., 2012). An adaptive stress response increases SNS activity and decreases PNS activity, and vice versa for adaptive recovery, thus both systems tend to be reciprocally coupled (Berntson et al., 1991).

Whereas physiological changes due to SNS activation only take seconds, HPA activation has a slower onset and longer duration. HPA axis activation results in the production of steroid hormones and is typically assessed by measuring its final product cortisol (Bauer et al., 2002). Much research has been devoted to understand the neurobiology of stress. However, most studies examined either the ANS or HPA axis in isolation, although interactional effects between both systems may obscure true effects when only one system is evaluated (Bauer et al., 2002). Also, many studies investigating the ANS focused on the PNS, even though the SNS and PNS are interrelated (Berntson et al., 2008). Therefore, this study examines both SNS and PNS parameters in conjunction with the HPA axis within a sample of traumatized adolescents.

The association between trauma and the SNS, or PEP, has not been extensively investigated. Some studies found increased PEP reactivity after traumatic events (Cohen et al., 2020), while others observed no relation (McLaughlin, Alves, et al., 2014). However, these studies were all conducted among non-clinical samples:

neither traumatic experiences nor posttraumatic stress were used as inclusion criteria. In contrast to the few studies that have examined the SNS, the relation between trauma and the PNS, in particular RSA, has received considerable attention. High RSA is considered a marker of self-regulatory capacity and indicates strong parasympathetic influence on the heart, which is considered adaptive (Porges, 2007). A meta-analysis showed an association between low RSA and trauma in adults, but in the few studies conducted among adolescents, effects were less strong (Campbell et al., 2019). Yet, basal RSA and RSA reactivity tend to be lower in clinical or at-risk samples as compared to healthy community samples and significant effects have been reported for low RSA and internalizing, externalizing, and cognitive problems among adolescents (Graziano & Derefinko, 2013). Together, these findings suggest that traumatic experiences may lead to an overactive SNS and blunted PNS reactivity.

Many studies have evaluated the impact of trauma on adolescents' HPA axis. Among studies that examined basal salivary cortisol (sC), many inconsistencies were reported, including both lower and higher sC (Trickett et al., 2011). These inconsistencies may result from variations in timing (DePasquale et al., 2019), severity (Ouellet-Morin et al., 2019), and type (Kuhlman et al., 2015) of trauma. However, these inconsistencies could also be due to the nature of sC measurements, which capture real-time cortisol levels and are subject to many fluctuations. An alternative is provided by cortisol measured in hair (hC), which captures long-term systemic cortisol exposure and is useful for measuring chronic stress (Russell et al., 2012). Yet, of the two studies examining hC and trauma among adolescents, one reported lower (Straub et al., 2017) and the other higher (Simmons et al., 2016) hC levels related to trauma. Due to these inconsistent outcomes for both sC and hC, an additional avenue of research that could provide insight lies in studies that investigate treatment effects on cortisol. Studies conducted among adults (Iglesias et al., 2015) and adolescents reported a decrease in hC after trauma treatment (Slopen et al., 2014). Although the extant evidence for alternations in basal HPA axis activity after trauma is scant, the reported intervention effects on hC suggest that trauma results in increased basal hC levels that – not unimportant – can be altered by effective treatment.

Studies on trauma and sC reactivity to acute stress reported consistently lower sC reactivity in relation to trauma among adolescents (Busso et al., 2017; Ouellet-Morin et al., 2019) and adults (Bunea et al., 2017). Although it might seem counterintuitive that trauma is related to higher basal levels of cortisol and lower cortisol reactivity, this could reflect down-regulation to acute stress due to chronic stress exposure (i.e., allostatic load; Bauer et al., 2002).

The present study is the first to investigate SNS (i.e., PEP), PNS (i.e., RSA) and HPA axis (i.e., cortisol) parameters among a clinical sample of traumatized adolescents and a healthy comparison group. Basal activity as well as acute reactivity to social stress were examined. Much research has been conducted examining the relations between trauma and the ANS and HPA axis separately, but these do not function in isolation, which is why research best assesses these systems together (Bauer et al., 2002). Only one study evaluated both systems together: in a community sample, traumatic events were associated with blunted SNS and HPA axis reactivity (Busso et al., 2017). Yet, the PNS was not included in this study, trauma was assessed in a non-clinical sample, and no comparison was made to a healthy control group.

Although research on PEP shows some inconsistency, most studies reported increased PEP reactivity (i.e., increased SNS reactivity) in relation to trauma. Since it is assumed that optimal performance requires reciprocal activation of the ANS branches (Berntson et al., 1991), we expect lower basal PEP (i.e., increased SNS activity) and increased PEP reactivity among traumatized adolescents. We expected lower basal RSA and RSA reactivity in traumatized adolescents. Regarding the HPA axis, based on previous research, we expect increased hC and blunted sC cortisol reactivity to stress compared to healthy controls.

METHODS

Sample characteristics

Traumatized participants: for the clinical sample, the present study used pre-test data from a randomized controlled trial (RCT) testing a game-based meditation intervention to decrease posttraumatic stress in traumatized adolescents. These participants (N = 77) were recruited in residential youth care institutions in the Netherlands. For detailed information on this study see Schuurmans and colleagues (2020).

Healthy controls: to obtain a comparison sample, healthy controls (N = 48) were recruited in the general community through schools and companies (intranet advertisement) in the Netherlands.

Inclusion criteria for both samples were as follows: (1) age 10 to 18 years; (2) being able to comprehend and speak Dutch; (3) active informed participant assent; and (4) active informed parental/legal guardian consent when participants are under the age of 16. An additional inclusion criterium for traumatized participants was: (5) clinical score (≥ 30) of posttraumatic symptoms on the Children's Revised Impact of Event Scale (CRIES-13; Verlinden et al., 2014). Exclusion criteria for the healthy controls based on parental information were: (1) diagnosis of a DSM disorder; and (2) current or recent psychotherapeutic treatment.

Procedure

This study was part of a project that included two studies: the current comparison study and a RCT (Schuurmans et al., 2020). Both studies were evaluated by the medical ethical committee Arnhem-Nijmegen which provided ethical review and approval under protocol NL58674.091.16. At time of admission to the residential institutions, adolescents filled in the CRIES-13 (Verlinden et al., 2014). We used these data to screen for potential participants. Participants' self-report questionnaires were administered through an interview. Mentor/parent-reported questionnaires were filled in by participants' mentors (clinical sample: the group care worker with whom they have the most contact) or parents (healthy control sample) and send to the researcher by post or e-mail. The testing sessions consisted of ANS measurements during rest and during a social stress task, saliva cortisol (sC) sampling before and after the stress task, and hair cortisol (hC) sampling.

At initial assessment, basal ANS parameters were measured while participants watched an aquatic video for five minutes (Piferi et al., 2000). The social stress task was an adapted version: the Trier Social Stress Task for Children (TRIER-C) (Buske-Kirschbaum et al., 1997) was combined with the Sing-a-Song Stress Test (SSST) (Brouwer & Hogervorst, 2014). We combined the speaking task with a song task rather than the traditional math assignment (Buske-Kirschbaum et al., 1997), to ensure comprehension for participants with low IQ. Participants received the introduction of a story and were told that they had five minutes to compose the end of the story before they would present their story for four minutes in front of a camera (Popma et al., 2006). Participants were recorded, allegedly for later assessment by a group of peers who would judge their performance. Then, participants were given a booklet with song texts and were told that they had to sing a song, also in front of the camera. Participants had thirty seconds to choose a song and had to sing the song aloud for thirty seconds. At the end of the testing session, participants received a gift voucher of €15. For detailed information on the measurement procedures, see (Schuurmans et al., 2020).

Participants received specific instructions for the measurement session: light breakfast, no caffeine, no intense exercise or smoking immediately before the session and no alcohol or drugs use 24 hours before the measurement. To control for these potential confounding variables, participants were asked about their intake of food/drinks, cigarette, alcohol and drugs in the 24 hours before the measurement. Participants were assured that their answers would only be used for research purposes and would not be communicated to their group care workers or parents.

Measures

Questionnaires

Exposure to traumatic events: the *Lifetime Incidence of Traumatic Events* (LITE) (Greenwald & Rubin, 1999) is a 16-item self-report questionnaire that asks participants to rate their exposure to 16 types of traumatic events that can be categorized as domestic (e.g., parental divorce), interpersonal (e.g., being robbed), and non-intentional (e.g., traffic accident). For each type of trauma exposure, a sum score was created. The LITE covers a broad range of potentially traumatic events of which many escape clinical detection and LITE scores have been found to predict posttraumatic symptoms (Greenwald & Rubin, 1999).

Exposure to abuse: the *Childhood Experience of Care and Abuse Questionnaire* (CECA.Q) (N. Smith et al., 2002) is an interview-questionnaire that asks participants to rate their exposure to four trauma categories: 'sexual abuse', 'physical abuse', 'emotional abuse', and 'parental antipathy/neglect'. For each type of trauma exposure, a sum score was created. The CECA.Q demonstrated good validity and reliability in both clinical and community populations (Smith et al., 2002).

Posttraumatic symptoms: the *Child Report of Posttraumatic Symptoms* (CROPS) (Greenwald & Rubin, 1999) and the *Parent Report of Posttraumatic Symptoms* (PROPS) (Greenwald & Rubin, 1999) are used to measure self- (e.g., 'I think about bad things that have happened') and mentor/parent-reported posttraumatic symptoms (e.g., 'My child had bad dreams or nightmares'). The CROPS and PROPS consist respectively of 24 and 32 items that are rated on a three-point scale of intensity ('none', 'some', or 'lots'). The validity and reliability of both questionnaires has been demonstrated to be adequate (Greenwald & Rubin, 1999).

Stress: levels of stress were assessed with the Depression Anxiety Stress Scales (DASS-21) (De Beurs et al., 2001). The stress scale consists of 7 four-scale items that measure self-reported stress and range from 'never' to 'almost always' (e.g., 'I get upset easily'). The DASS-21 has good validity and reliability (De Beurs et al., 2001).

Physiological measures: ANS

ANS measures were performed using electrocardiogram (ECG) and impedance cardiography (ICG) registration by the VU University Monitoring System (VU-AMS) (De Geus et al., 1995). Five electrodes were placed on participants' chest and two on the back. Recordings were manually inspected and analyzed with the Data Analysis and Management Software (VU-DAMS) program version 4.0 [VU University, Amsterdam, the Netherlands]. PEP expressed in msec was derived from combined ECG and ECG recordings. RSA values were set as missing when > 50% of the recording was marked as 'irregular' by the VU-DAMS software. RSA can be influenced by respiration rate (RR) independently from PNS activity, so respiration rate (RR) (derived from the thorax impedance) was included as a covariate for RSA.

Basal ANS activity: ECG recordings during the 5-minute aquatic video were used to obtain basal ANS measures during rest.

ANS reactivity to acute stress: the following ECG recordings during the stress task were used to evaluate ANS reactivity: [1] anticipation, [2] performing speech task, [3] anticipation song task, [4] performing song task, and [5] recovery. The area under the curve with respect to the increase (AUC_i) and area under the curve with respect to the ground (AUC_g) were calculated. AUC_i represents sensitivity of the stress system, pronouncing changes over time, while AUC_g represents total hormonal output (Pruessner et al., 2003). ANS AUC were calculated using recordings 1 to 5.

Physiological mepasures: HPA axis

Basal HPA axis activity: hC levels pg/mg hair were derived to obtain a measure of basal HPA activity. Hair samples were cut as close to the scalp as possible from a posterior vertex position. Samples were taped on paper and stored in closed envelopes until sent collectively to the laboratory of endocrinology of the Erasmus Medical Center, Rotterdam, the Netherlands. At least 5 mg of the most proximal 2 cm of each hair sample was used for analysis – representing basal hC over the 8 weeks before the hair sample was taken. Hair samples were washed in LC-MS grade isopropanol and after solid phase extraction, hair cortisol was quantified by liquid chromatography-tandem mass spectrometry (LCMS) (Noppe et al., 2015).

HPA axis reactivity: to evaluate HPA reactivity, sC samples (nmol/l) were collected before and after the stress task. Samples were collected between 13.00PM and 17.00PM using Cortisol Salivette collection tubes (Sarstedt, Nümbrecht, Germany). To establish a pre-task resting baseline, sample collection started at least 20 minutes after participants entered the measurement room. Six sC samples were collected: [1] twenty minutes before the stress task started (-20), [2] immediately before (pre), [3] immediately after (post), and [4] ten (+10), [5] twenty (+20), and [6] forty (+40) minutes after the stress task had ended. Due to latency-time, cortisol AUC were calculated using samples 2 to 5, with reference to sample 2, since stressors cause an increase in cortisol levels that peaks after approximately 15 minutes (Bauer et al., 2002). Samples were stored at -20 degrees Celsius until sent collectively to the laboratory of endocrinology of the Erasmus Medical Center, Rotterdam, the Netherlands. Cortisol levels were measured using the LC-MS/MS method with the CHS MSMS Steriods Kit (Perkin Elmer, Turku, Finland) containing $^2H_3$-cortisol as internal standard. Chromatographic separation was performed on a Waters (Milford, MA, USA) Acquity UPLC HSS T3 1.8µm column and quantified by tandem mass spectrometry using a Xevo TQ-S system (Waters, Milford, MA).

Statistical analyses

Traumatized and non-traumatized participants were compared on demographics and trauma exposure using chi-square and t-tests. Neurobiological parameters were compared between both samples with correlations and multivariate analysis of variance (MANOVA) to account for multiple comparisons and covariates on the basal activity for PEP, RSA, and hC and for the AUC calculated for PEP, RSA, and sC. Repeated analyses of variance (ANOVA) and covariance (ANCOVA) to account for covariates with ‘group’ (traumatized adolescents vs. healthy controls) as between subjects factor and 'time' (consecutive recordings or samples) as within-subjects factor were conducted to assess differences between the two samples in PEP, RSA, sC reactivity and subjective distress during the social stress task. Interaction effects between 'time' and 'group' were further analyzed by conducting difference contrast tests, that is, comparing the values of a sample at a certain time point to all previous ones.

Potential covariates were smoking (number of cigarettes in the past 24 hours), alcohol (number of consumptions in the past 24 hours) and caffeine use (number of consumptions in the past 24 hours) in the 24 hours before testing, lifestyle smoking (average number of cigarettes a day), alcohol use (average number of consumptions a week), sporting behavior (average hours a week), eating behavior (average daily meals and snacks), medication use, comorbid psychological and physiological disorders. Additional covariates considered for salivary cortisol were hormonal contraception, menstrual cycle phase, season (as cortisol peaks in spring), time of testing (as cortisol concentrations decrease during the day), storage time and participants' age. For hair cortisol, additional covariates were hair treatment (i.e., dying/bleaching; yes/no) and hair washing (times a week).

An a priori power analysis for repeated measures ANOVA with a small-to-medium effect size of d = .30 estimated a sample size of 72 with 36 participants in each condition (Schuurmans et al., 2020). In total 77 clinical participants were recruited for the RCT and used as a convenience sample for the current study. We aimed to recruit 45 healthy participants as there were no resources to recruit more participants for the current study. Post-hoc analyses (Levene's Test) to test for assumption violation (Field, 2005) and an ANCOVA post-hoc power analysis will be conducted.

RESULTS

Table 1 shows characteristics of the two samples on psychopathology and trauma exposure. Traumatized adolescents and healthy controls were significantly different on all trauma-related outcomes (all $p < .05$). Traumatized adolescents scored higher on posttraumatic symptoms and stress than healthy controls. Notably, for traumatized adolescents, frequency rates for emotional abuse, neglect, domestic, interpersonal, and non-intentional trauma were all over 85%, with an average number of events over 100 for domestic and interpersonal trauma, indicating the severity of the traumatization.

The clinical sample has spent on average 47.33 months (SD = 41.48) in residential institutions. The clinical and healthy controls sample were not significantly different in age (traumatized adolescents: mean age = 15.09, SD = 1.94; controls: mean age = 14.43, SD = 2.35, p = .112), but they were in gender (traumatized: male 59.7%; controls: male 48.3%, p = .041). Therefore, gender was included as covariates in the analyses. For parsimony, only covariates that were significant were included in the models.

Data inspection revealed missing data (5.08% for RSA, 3.73% for PEP, 16.9% for hC, 2.84% for sC) due to technical issues, movement during recording (PEP and RSA), not enough saliva (sC) or hair (hC), or laboratory processing problems (sC and hC). Data were missing at random, providing support for imputing the missing data using full information maximum likelihood estimation for Markov Chains (Graham, 2009). The PEP, RSA, sC and hC data were positively skewed and $\log^{10}$ transformed (Houtveen et al., 2002). For reasons of physiological meaningfulness, the graphical representation of data in Figure 1 and means and SDs for hC and basal PEP, and RSA in Table 2 show absolute values instead of transformed values. AUC values in Table 2 represent standardized means and SDs. Analysis outcomes with imputed, transformed data are reported. All analyses were conducted with completers-only data too. These results showed minimal differences and led to the same statistical outcomes. For the sake of parsimony, the ANCOVA analyses were executed in one model. Due to missing data for the PEP covariate smoking in the past 24 hours, three participants (two clinical, one control) were excluded from the ANCOVA analyses. RSA, sC and hC analyses were also run separately with all participants included which led to the same statistical outcomes. See Figure 1 for a Flow chart including missing data for all analyses.

Although sample sizes of the two groups were uneven, Levene's Tests were not significant; thus assumptions with respect to unequal sample sizes were not violated. Post-hoc ANCOVA power analyses showed 78.20% statistical power for to detect a η2p = .05 difference with 122 participants.

Bivariate correlations for all outcomes are presented in Table 2. Of note, sample was positively related to all questionnaire outcomes, indicating higher scores of the traumatized sample compared to healthy controls. Sample was also positively related to basal hC, but negatively to most other physiological outcomes. This indicates that although traumatized adolescents have higher levels of hC compared to healthy controls, they score lower on most other physiological outcomes. As expected, basal PEP and RSA outcomes showed strong positive relations with the corresponding AUC_g outcomes. Basal hC were related to sC AUC_g, but not to sC AUC_i.

Table 1. Psychopathology and Trauma Exposure for Traumatized Adolescents and Healthy Controls.

	Traumatized Adolescents		Healthy Controls		Group Difference
Psychopathology	*M*	*SD*	*M*	*SD*	*p*
Posttraumatic symptoms					
Self-report	24.41	9.86	12.27	5.99	< .001
Mentor/parent-report	26.62	10.13	11.63	6.41	< .001
Stress	8.92	4.71	3.22	2.80	< .001
Trauma Exposure	*n*	%	*n*	%	
Domestic trauma	73	98.60%	5	10.60%	< .001
Interpersonal trauma	63	85.10%	13	27.60%	< .001
Non-intentional trauma	74	100%	39	83%	< .001
Sexual abuse	21	27.30%	0	0%	< .001
Physical abuse	22	17.70%	0	0%	< .001
Emotional abuse	70	90.90%	0	0%	< .001
Neglect	76	98.70%	0	0%	< .001
Parental loss Y/N	6	8.60%	0	0%	< .039
Parental separation Y/N	47	66.20%	0	0%	< .001
Parental psychiatry Y/N	30	44.10%	0	0%	< .001
Trauma Exposure	*M*	*SD*	*M*	*SD*	
Domestic trauma	116.82	518.39	.15	.47	.005
Interpersonal trauma	103.64	504.36	.32	.56	.016
Non-intentional trauma	14.41	18.29	6.75	8.58	.002
Sexual abuse	2.30	4.19	0.00	-	< .001
Physical abuse	.83	1.3	0.00	-	< .001
Emotional abuse	19.08	19.69	0.00	-	< .001
Neglect	38.81	11.52	0.00	-	< .001

Note: M = mean; SD = standard deviation. Mean scores on domestic, interpersonal, and non-intentional trauma represent the total number of events in a lifetime. Other outcomes represent mean scores on trauma severity measures ranging: 0-7 for sexual abuse; 0-6 for physical abuse; 0-51 for emotional abuse; and 0-48 for neglect.

Clinical group traumatized adolescents	**Healthy control group**
Assessed for eligibility (n = 135) Excluded (n = 53) • Current or recent trauma treatment (n = 19) • Youth/parent declined participation (n = 11) • Would leave institution soon (n = 13) • Negative clinician advice (n = 10)	**Assessed for eligibility (n = 48)**
↓	↓
Included in study (n = 77)	**Included in study (n = 48)**
↓	↓
ANCOVA PEP, RSA, hC (n = 75) *Covariate PEP: smoking in the past 24 hours.* *Covariate RSA: RR.* Excluded (n = 2) • Missing data covariate smoking.	**ANCOVA PEP, RSA, hC (n = 47)** *Covariate PEP: smoking in the past 24 hours.* *Covariate RSA: RR.* Excluded (n = 1) • Missing data covariate smoking.
Repeated-measures ANOVA PEP (n = 74) *Covariate: Caffeine use in the past 24 hours.* Excluded (n = 3) • Missing data covariate caffeine use.	**Repeated-measures ANOVA PEP (n = 39)** *Covariate: Caffeine use in the past 24 hours.* Excluded (n = 9) • Missing data covariate caffeine use.
Repeated-measures ANOVA RSA (n = 77) *Covariate: RR.*	**Repeated-measures ANOVA PEP (n = 48)** *Covariate: RR.*
Repeated-measures ANOVA sC (n = 77) *No significant covariates.*	**Repeated-measures ANOVA sC (n = 48)** *No significant covariates.*

Figure 1. Flow chart

Table 2. Bivariate Correlations for All Outcomes.

		1	2	3	4	5	6	7	8	9	10	11	12
1	Sample	-											
2	CROPS	.59*	-										
3	PROPS	.66*	.58*	-									
4	Stress	.58*	.86*	.57*	-								
	Basal ANS												
5	PEP	-.19*	-.01*	-.07*	-.06*	-							
6	RSA	-.24*	-.17*	-.26*	-.23*	-.07*	-						
	ANS reactivity												
7	PEP AUC_i	-.14*	-.05*	-.03*	-.06*	.25*	.08*	-					
8	PEP AUC_g	-.22*	-.02*	-.07*	-.07*	.96*	.04*	.51*	-				
9	RSA AUC_i	.14*	.00*	.02*	.04*	.09*	.56*	.10*	.05*	-			
10	RSA AUC_g	-.21*	-.20*	-.28*	-.25*	-.03*	.83*	.02*	.14*	-.01*	-		
	Basal HPA												
11	hC	.35*	.18*	.24*	.28*	.00*	.07*	.04*	.13*	-.08*	.04*	-	
	HPA reactivity												
12	sC AUC_i	-.24*	-.08*	-.21*	-.06*	.10*	.25*	.09*	-.02*	-.17*	.19*	.00*	-
13	sC AUC_g	-.24*	-.14*	-.11*	-.08*	.05*	.04*	.05*	-.01*	-.06*	.01*	.37*	.07*

Note. Sample was coded as: 0 = healthy controls, 1 = traumatized adolescents. ANS: autonomic nervous system; AUC_i: area under the curve with respect to the increase; AUC_g: area under the curve with respect to the ground; PEP: pre-ejection period; RSA: respiratory sinus arrhythmia; HPA: hypothalamic-pituitary-adrenal; hC: hair cortisol; sC: salivary cortisol.

Basal ANS activity

Table 3 shows means and standard deviations for basal ANS parameters and the statistics for group differences. Traumatized adolescents showed significant lower PEP and RSA parameters compared to healthy controls.

Acute ANS activity to stress

Table 3 shows PEP and RSA AUC outcomes for the two samples. A graphic representation of the PEP and RSA reactivity patterns by sample is given in Figure 2 and 3. Repeated-measures ANOVA on PEP reactivity revealed a significant main effect of time, $F(5, 106) = 7.92$, $p < .001$, $\eta 2p = .27$, a significant effect of group, $F(1, 106) = 11.58$, $p = .001$, $\eta 2p = .10$ and a significant group-time interaction, $F(5, 106) = 4.63$, $p = .001$, $\eta 2p = .18$. The two samples significantly differed on all recording samples. Caffeine use in the past 24 hours before measurement was included as a covariate for PEP. For RSA we found a significant main effect of time, $F(5, 118) = 6.61$, $p < .001$, $\eta 2p = .22$, and group $F(1, 122) = 4.38$, $p < .038$, $\eta 2p = .04$, but no significant group-time interaction, $F(5, 118) = .90$, $p = .485$, $\eta 2p = .04$. RR was included as a covariate for RSA.

Basal HPA axis activity

Traumatized adolescents had significant higher levels of hC compared to healthy controls (see Table 3).

Acute HPA reactivity to stress

Table 3 shows sC AUC outcomes for the two samples. Figure 4 shows the means for the six sC samples for the two groups. Repeated measures ANOVA revealed a significant main effect of time, $F(5, 118) = 7.27$, $p < .001$, $\eta 2p = .24$ and a significant group × time interaction, $F(5, 118) = 8.04$, $p < .001$, $\eta 2p = .25$, indicating that the sC response curve differed between the two groups. As is shown in Figure 4, while healthy controls do show a sC response to the stressor, there was no sC response among traumatized adolescents. There was no effect of group, $F(1, 112) = .02$, $p < .903$, $\eta 2p = .00$. The interaction effect was attributable to significant effects for sample 1 (-20) and 4 (+10): traumatized adolescents exhibit higher sC levels twenty minutes before the stress task and lower sC levels ten minutes after the task.

Table 3. Neurobiological Parameters of Traumatized Adolescents and Healthy Controls.

	Descriptives				Group Differences		
	Traumatized Adolescents		Healthy Controls				
	Mean	SD	Mean	SD	*F*	*p*	η2p
Basal ANS activity							
PEP	90.02	18.99	96.85	12.88	9.18	.003	.07
RSA	70.45	41.98	85.47	39.28	4.97	.028	.04
ANS reactivity							
PEP AUC_i	-.10	1.15	.17	.65	5.16	.025	.04
PEP AUC_g	-.16	1.12	.27	.71	10.17	.002	.08
RSA AUC_i	.06	.76	-.10	1.30	.46	.500	.00
RSA AUC_g	-.12	1.04	.20	.91	2.12	.148	.02
Basal HPA activity							
hC	2.29	1.33	1.70	.82	3.95	.049	.03
HPA reactivity							
sC AUC_i	-.20	.83	.32	1.17	8.03	.005	.06
sC AUC_g	-.16	.82	.27	1.20	5.07	.026	.04

Note. ANS: autonomic nervous system; AUC_i: area under the curve with respect to the increase; AUC_g: area under the curve with respect to the ground; PEP: pre-ejection period; RSA: respiratory sinus arrhythmia; HPA: hypothalamic-pituitary-adrenal; hC: hair cortisol; sC: salivary cortisol. All *df* (1, 122). hC is measured as pg/mg. sC is measured as nmol/l. Basal PEP, RSA, and hC are absolute values. AUC are standardized values.

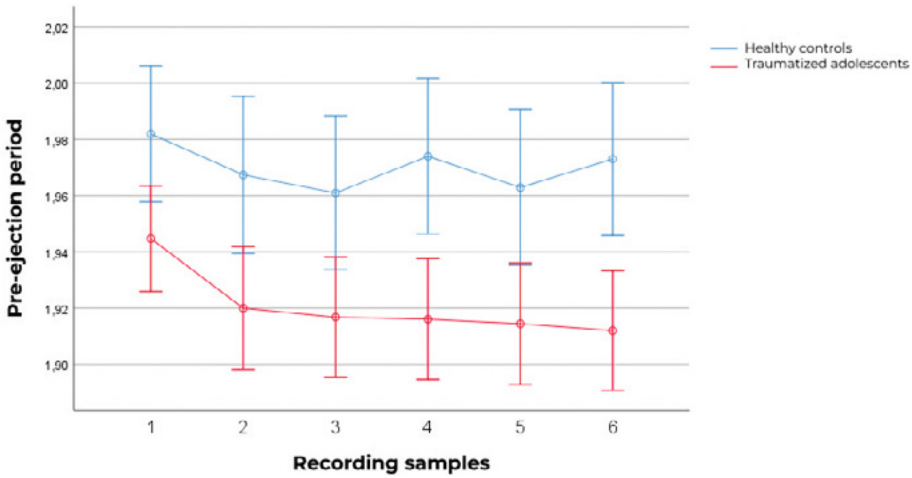

Figure 2. PEP reactivity during recording samples. Means and standard errors.
Note. Recording samples represent [1] anticipation, [2] performing speech task, [3] anticipation song task, [4] performing song task, and [5] recovery.

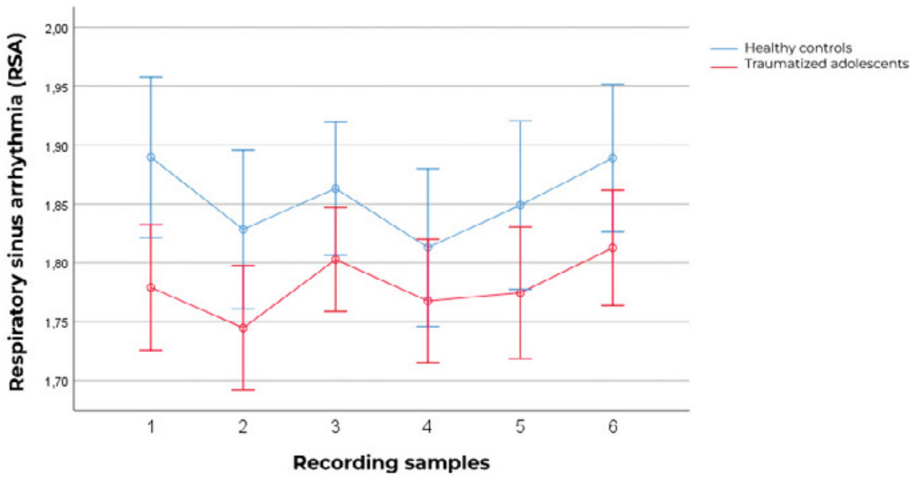

Figure 3. RSA reactivity during recording samples. Means and standard errors.
Note. Recording samples represent [1] anticipation, [2] performing speech task, [3] anticipation song task, [4] performing song task, and [5] recovery.

2

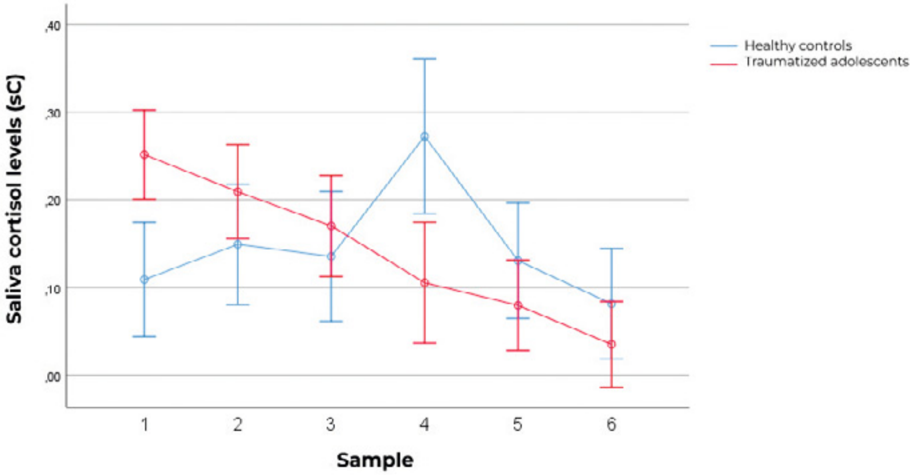

Figure 4. Saliva cortisol (sC) reactivity during recording samples. Means and standard errors. *Note*. Samples were taken [1] twenty minutes before the stress task started (-20), [2] immediately before (pre), [3] immediately after (post), and [4] ten (+10), [5] twenty (+20), and [6] forty (+40) minutes after the stress task.

DISCUSSION

Key findings

The current study evaluated SNS (i.e., PEP), PNS (i.e., RSA) and HPA axis (i.e., cortisol) parameters among a clinical sample of traumatized adolescents and comparison sample of healthy adolescents. Basal activity as well as acute reactivity to social stress were examined. Although research on PEP shows some inconsistency, most studies reported increased PEP reactivity (i.e., increased SNS reactivity) in relation to trauma. Since it is assumed that optimal performance requires reciprocal activation of the ANS branches (Berntson et al., 1991), we expect lower basal PEP (i.e., increased SNS activity) and increased PEP reactivity among traumatized adolescents. We expected lower basal RSA and RSA reactivity in traumatized adolescents. Regarding the HPA axis, based on previous research, we expect increased hC and blunted sC cortisol reactivity to stress compared to healthy controls.

Differences between traumatized adolescents and healthy controls were evident on several dimensions. Findings regarding basal ANS activity indicated that traumatized adolescents showed both lower PEP and RSA parameters during rest compared to healthy controls. For ANS AUC outcomes, traumatized adolescents showed higher PEP AUC_g, which is likely due to the difference in basal PEP, since the samples did not differ on PEP AUC_i. Reactivity pattern analyses revealed that healthy controls showed blunted PEP reactivity during both the anticipation period for the singing task and the recovery period immediately after the stress task, indicating faster recovery than the clinical sample. No differences were found for RSA reactivity between both samples.

To our knowledge, this is the first study that reports on dysregulated basal PEP parameters in traumatized adolescents. Heightened SNS reactivity increases emotion-driven impulsivity and facilitates vulnerability for at-risk behavior (Peters et al., 2018), which characterizes many traumatized adolescents. The finding that traumatized adolescents exhibit increased PEP reactivity to stress is in line with previous studies on early adversity in community samples (Cohen et al., 2020; Ellis et al., 2005; Oosterman et al., 2010). One study that reported no relation between PEP reactivity and trauma was conducted in a sample that exhibited comorbid externalizing problems (McLaughlin, Alves, et al., 2014). This might have obscured relations, since externalizing behavior is associated with blunted SNS reactivity (Beauchaine et al., 2008).

The finding of decreased basal RSA in traumatized adolescents is in line with previous research (Graziano & Derefinko, 2013) and confirms our hypothesis. Low basal RSA is related with heightened emotional reactivity, poor attentional and inhibitory control, and psychopathology (McLaughlin et al., 2015; McLaughlin, Sheridan, et al., 2014; Porges, 2007). In contrast to expectations, we did not find significant differences in RSA *re*activity between traumatized adolescents and healthy controls, while this has been reported in past research (Graziano & Derefinko, 2013; McLaughlin et al., 2015; McLaughlin, Alves, et al., 2014). In clinical samples, higher basal RSA and RSA reactivity have also been associated with increased psychopathology (Graziano & Derefinko, 2013). The relation between trauma and RSA reactivity may be complex and potentially nonlinear: moderate RSA reactivity to a stressor may be a more adaptive response than no reactivity (i.e., hypo-arousal), but extreme reactions might indicate over-reactivity to environmental threats (i.e., hyper-arousal) (Corrigan et al., 2011).

Although this is the first study to document on dysregulated PEP parameters among traumatized adolescents, these findings are in line with research in an at-risk, low-income community sample that showed that sympathetically-oriented stress responses could distinguish between adolescents with and without posttraumatic symptoms (Cohen et al., 2020). Interestingly, PEP reactivity analyses showed that healthy controls were able to recover quickly after the stressor disappeared, whereas prolonged sympathetic activation was observed in traumatized adolescents. Recovery after the stressor has ended is an essential part of an adaptive and healthy stress responding (Linden et al., 1997). Specifically, prolonged recovery increases susceptibility to stress, whereas quick recovery is seen as an adaptive response (Bugental, 2004).

We found that traumatized adolescents had higher levels of hC than healthy controls, a finding that is consistent with results in adolescents and adults who experienced traumatic events (Schalinski et al., 2015; Simmons et al., 2016). For sC reactivity, however, traumatized adolescents showed blunted reactivity (both AUC_i and AUC_g) and the reactivity patterns analysis revealed the absence of sC responsivity towards the stressor. Blunted cortisol responses in traumatized adolescents are reported by other studies as well (Busso et al., 2017; Ouellet-Morin et al., 2019). This provides support for the adaptive calibration model, that states that HPA axis responses to stress can be recalibrated according to environmental circumstances (Ellis & Del Giudice, 2019).

Intuitively, it could be argued that participants with higher levels of basal cortisol levels (i.e., long-term cortisol exposure) also show a stronger cortisol response to the stress task. However, similar results (i.e., increased hC levels and blunted sC response towards stress) have been found in adults with childhood trauma (Schalinski et al., 2015). This could be due to recent stress exposure. Levels of hC represent systemic cortisol exposure in the months before the measurement. Our traumatized sample was recruited in residential institutions, which tend to be stressful living environments with high instability and uncertainty (Cohen et al., 2012). Although we did not measure recent stress exposure, it may be that our traumatized sample was also exposed to more recent stressful events than our sample of healthy controls, resulting in the increased hC levels for traumatized adolescents. This might explain the finding of lower hC in traumatized adolescents by Straub and colleagues (2017). They included participants who had experienced or witnessed an accident or case of emergency and one of their inclusion criteria was 'safe current living conditions'. Their sample might not generalize to the population of adolescents who lives in residential institutions, since the experience of a single non-interpersonal traumatic event is substantially different from prolonged neglect or abuse by caregivers.

Our finding that stress responses in traumatized adolescents include activation of the ANS but not the HPA axis, fits with the interactive model that states that low reactivity on one system combined with high reactivity on another system is associated with increased risk on emotional and behavioral problems (Bauer et al., 2002). It also fits with the Adaptive Calibration Model that proposes the neurobiological stress systems show conditional adaptation (Ellis & Del Giudice, 2019). Children who are raised under high-stress conditions can at first become hypervigilant and responsive for stressors (hyperarousal). After a while, due to repeated and prolonged activation of the physiological stress systems (allostatic load), they shift to low stress responsivity (hypoarousal). Hyporesponsivity is characterized by a blunted HPA axis response (Busso et al., 2017; Ouellet-Morin et al., 2019) and PNS-dominated activation of the ANS (Corrigan et al., 2011), which is in line with our findings.

Strengths and limitations

The results of this study add to the existing literature in several ways. To our knowledge, this is the first study to examine not only basal activity, but also reactivity to stress of both the ANS and HPA axis in a clinical sample of traumatized adolescents in residential care. A particular strength of this study is the incorporation of both the ANS and the HPA axis and also, for the ANS, sympathetic as well as parasympathetic influences were measured. Including the SNS and PNS is important since stress responses can result in high or low sympathetic activity and high or low parasympathetic activity (Berntson et al., 1991). Previous studies on the relations between traumatic experiences and the ANS or HPA axis were conducted in community samples and focused on one system – either the ANS or HPA axis – at a time. Our traumatized sample consisted of adolescents admitted to residential youth care. This is a well-suited clinical population for the aim of this study, since over 90% of adolescents in residential care have experienced traumatic events (Collin-Vézina et al., 2011).

Our findings should be interpreted in the light of several limitations. First, although PEP is a valid measure for SNS activation, another marker of the SNS is skin conductance. However, skin conductance appears most suitable for measuring responses to stimuli that are presented for milliseconds to seconds, rather than longer stress tasks that last for minutes to hours (Popma et al., 2006) and does not represent cardiac activity but a different organ system, therefore we did not include skin conductance.

Second, a post-hoc power analysis showed that our study was slightly underpowered (< .80%) for the ANCOVA analyses, increasing the risk for Type II errors. However, we were able to detect significant effects on all ANCOVA outcomes except for the RSA AUC outcomes. This was in line with effects that were detected with the repeated-measures ANOVA outcomes (no significant group-time interaction for RSA). Thus, it might be safe to assume that the non-significant ANCOVA outcomes for RSA AUC resemble the true outcome of this data set.

Third, although our stress task has shown to be highly effective (Brouwer & Hogervorst, 2014; Buske-Kirschbaum et al., 1997), we did not perform a placebo test to verify that the observed stress reactions are indeed social stress reactions and no results from, for example, cognitive demands (Het et al., 2009). Yet, we specifically combined the speaking task with a song task rather than the traditional math assignment to prevent cognitive demands. Even in case there would be any secondary effects, it is expected that this would affect both samples and thus would not affect our outcomes.

Fourth and final, we considered a variety of potential covariates, but the relationship between neurobiological stress systems and behavior is complex and might be affected by variables not included in this study, such as the timing of traumatic events in relation to puberty onset (DePasquale et al., 2019), the amount of time that has passed since the events (Weems & Carrion, 2007), recent stress exposure (Bendezú & Wadsworth, 2017), and type of trauma (Kuhlman et al., 2015). The inclusion of all these potential moderators was beyond the scope of this study since valid assessment would have required complex additional measures. Yet, youth in residential care are characterized by trauma exposure that started at a young age (Briggs et al., 2012; Collin-Vézina et al., 2011; Van der Kolk, 2005), thus we may assume that these events started before their puberty onset. Regarding the timing and type of traumatic events, Weems and Carrion (2007) consider traumatic events that have taken place longer than one year ago as distal events. Since our clinical participants on average have spent almost four years in residential care, and most perpetrators are the youths' parents or caregivers (Connor et al., 2004), we assume that their traumatic experiences took place more than one year ago and can be considered distal events. The majority of our traumatized participants experienced domestic trauma, interpersonal trauma, non-intentional trauma, emotional abuse and neglect (frequency rates all > 85%). The experience of other types of trauma such as sexual (frequency rate = 27.30%) and physical abuse (frequency rate = 17.70%) may indeed have led to small subsamples. Yet, these subsamples were small and moderator analyses would have been underpowered, why it is not expected that type of trauma would have affected our outcome. Yet, its potential effect on neurobiological outcomes remains a great avenue for future research to pursue.

Lastly, we do not expect that effects of recent stress exposure may have affected our outcomes, since all clinical participants lived in residential institutions. Although residential care provides an often chaotic living environment (Cohen et al., 2012) which could have led to increased recent stress exposure. However, if this is the case, this should have equally affected all clinical participants and should be considered characteristic for the sample. Furthermore, body mass index (BMI) should be considered as non-trauma related covariate (Bose et al., 2009). Even though we did not measure participants' BMI, we did include sporting and eating behavior as potential covariates, which are highly correlated with adolescents' weight (D'Addesa et al., 2010) and did not significantly affect our outcomes.

Implications and conclusion

From a clinical perspective, it is important to gain insight in how early traumatic experiences can affect neurobiological stress responses. As such, this study provides evidence for alterations in both the ANS and HPA axis. PEP is a marker that rarely has been studied in this population, although it is relatively simple and inexpensive to obtain PEP, compared to, for example, cortisol. Hence, if confirmed in other studies, PEP has the potential to become a clinically useful marker of stress sensitivity and may act as a target for intervention, because pretreatment neurobiological parameters can be predictive of responses to trauma-focused treatment (Lipschutz et al., 2017).

Results on ANS parameters showed that traumatized adolescents, compared to healthy controls, exhibited significantly higher sympathetic and lower parasympathetic activation during rest, and increased sympathetic reactivity to acute stress. Outcomes on HPA parameters indicated that traumatized adolescents showed increased HPA activity during rest and blunted HPA reactivity to acute stress as compared with healthy controls. These findings underscore the relation between alternated stress response systems after trauma and indicate that neurobiological markers might contribute to a better understanding of the underlying mechanisms of the development, persistence, and prognosis of posttraumatic stress. Ultimately, this could lead to the development of more effective interventions.

Chapter 3

Validation of the Empatica E4 wristband to measure heart rate variability (HRV) parameters: A comparison to electrocardiography (ECG)

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ABSTRACT

Wearable monitoring devices are an innovative way to measure heart rate (HR) and heart rate variability (HRV), however, there is still debate about the validity of these wearables. This study aimed to validate the accuracy and predictive value of the Empatica E4 wristband against the VU University Ambulatory Monitoring System (VU-AMS) in a clinical population of traumatized adolescents in residential care.

A sample of 345 recordings of both the Empatica E4 wristband and the VU-AMS was derived from a feasibility study that included fifteen participants. They wore both devices during two experimental testing and twelve intervention sessions. We used cross-correlations, Mann-Whitney tests, difference factors, Bland-Altman plots, and Limits of Agreement to evaluate differences in outcomes between devices.

Significant intraclass correlations were found between Empatica E4 and VU-AMS recordings for RR, HR, SDNN, RMSSD, LF, HF, and LF/HF recordings. There was a significant difference between the devices for all parameters but HR, although effect sizes were small for SDNN, LF, and HF. For all parameters but RMSSD, testing outcomes of the two devices led to the same conclusions regarding significance.

The Empatica E4 wristband provides a new opportunity to measure HRV in an unobtrusive way. Results of this study indicate the potential of the Empatica E4 as a practical and valid tool for research on HR and HRV under non-movement conditions. While more research needs to be conducted, this study could be considered as a first step to support the use of HRV recordings provided by wearables.

Abbreviations

ANS	autonomic nervous system
CC	cross-correlations
ECG	electrocardiography
HF	high frequency
HR	heart rate
HRV	heart rate variability
LF	low frequency
LF/HF	ratio between low and high frequency
NN	normal-to-normal
PNS	parasympathetic nervous system
SD	standard deviation
SDNN	standard deviation of the NN interval
SNS	sympathetic nervous system
RMSSD	root mean squared differences of successive difference of intervals

INTRODUCTION

The past two decades have witnessed an increase in psychophysiological studies that incorporate heart rate (HR) and other autonomic nervous system (ANS) parameters. In particular heart rate variability (HRV) has become the focus of psychophysiological research since it provides several parameters of the parasympathetic nervous system (PNS; Chapleau & Sabharwal, 2011). These parameters serve as an index of an individual's physiological reactivity to stress. Stress activates the sympathetic nervous system (SNS), responsible for high arousal including the fight-or-flight response, whereas the PNS facilitates the rest and digest response. Both branches are essential for the immediate stress regulatory response of the body (De Looff et al., 2018). The PNS is associated with self-regulation aspects of cognition, affection, and social behavior (McCrathy & Shaffer, 2015).

Most traditional devices that measure ANS parameters are based on electrocardiogram (ECG) recordings, such as the Biopac (Biopac ECG Module, Goleta, CA) or the VU University Monitoring System (VU-AMS; Vrije Universiteit, Amsterdam, the Netherlands). The VU-AMS is a lightweight ECG device for ambulatory assessment that is considered to be a 'gold standard' (De Geus et al., 1995; Willemsen et al., 1996). Although the VU-AMS provides excellent opportunities for ambulatory measurements in real-life contexts, application of the electrodes and setup of the device needs to be done by an expert. Simpler and less invasive monitoring systems such as wearable wristbands have been developed as a more convenient way to measure physiological parameters. Recent advances in technology, and in particular the development of wearable monitoring devices, have provided both researchers and lay people with a simple, non-invasive way to measure HR. The new generation of health monitoring devices consists of easy wearable devices that are worn as a smartwatch. Ideally, these wearables are non-intrusive, robust to movement, and highly accurate (García-González et al., 2015). The use of these wearable wristbands in healthcare yields high expectations, but it is unclear whether these expectations are warranted (Garbarino et al., 2014). There are several commercially available wristbands that potentially provide a range of HRV parameters, such as the Empatica E4 wristband (Garbarino et al., 2014; McCarthy et al., 2016; Ollander et al., 2017), the Polar watch (Caminal et al., 2018; Giles et al., 2016), and the Fitbit watch (de Zambotti et al., 2016; Diaz et al., 2015; Kang et al., 2017) among others. These devices provide a potentially simple and promising tool for data acquisition in both research and clinical studies (Jarczok et al., 2013; Kamath et al., 2016; Trimmel et al., 2015; Trotman et al., 2018), but are artefact prone due to movement (De Looff et al., 2018; Jarczok et al., 2013). Due to their non-invasive way of monitoring, these devices are in particular suitable for vulnerable populations such as clinical patients.

Although the reliability and validity of the VU-AMS to obtain HRV parameters has been established (De Geus et al., 1995; Willemsen et al., 1996), there is still debate on the validity of wearables as HRV monitoring systems. The use of these wearables in real-life is in particular challenging as there is considerable amount of movement, temperature fluctuation, and diurnal variation in HRV that could influence the recordings and subsequently the utility of the data (De Looff et al., 2018; Kamath et al., 2016). Validation studies are critical to ensure the accuracy, reliability and limitations of wearables before recommending their widespread adoption as a research tool. Studies testing the Polar V800 (Caminal et al., 2018; Giles et al., 2016) and the FitbitChargeHR™ (de Zambotti et al., 2016) demonstrated that HR and HRV recordings provided by wearables can be highly comparable and show high agreement with those of ECG systems.

Another type of wearable is the Empatica E4 wristband. Although previous studies suggested that Empatica E4 recordingse are comparable to ECG (McCarthy et al., 2016; Ollander et al., 2017; van Lier et al., 2020; Y. Zheng & Poon, 2016), these studies were no rigorous validation studies and had several limitations. While all compared the Empatica E4 to ECG, none of these studies used an ambulatory gold standard instruments such as the VU-AMS as reference device (De Geus et al., 1995; Willemsen et al., 1996). Second, despite its potential effect on the detection of stress and emotion (Picard et al., 2015), only Van Lier and colleagues (2020) provided details about the application of the Empatica E4 wristbands. They attached the Empatica E4 on participants' left wrists, so they were unable to make a comparison of different measurement conditions (e.g., left/right hand, dominant/non-dominant hand). Third, most of these studies included only a few time-domain ANS parameters such as HR and RMSSD. Only Ollander and colleagues (2017) included frequency-domain measurements too. None of the previous studies included SDNN, although SDNN is considered the best parameter for medical stratification of cardiac risk (Shaffer & Ginsberg, 2017). Fourth and final, the studies of McCarthy and colleagues (2016), Ollander and colleagues (2017), and Zheng and Poon (2016) were conducted with small sample sizes ranging from one to seven participants. Only the study of Van Lier and colleagues (2020) was adequately powered, but their sample consisted of University students only. In applied research, external validity is critical. Because of their non-intrusiveness, wearables are a promising tool for use in clinical research. Yet, it is important to test the validity of these tools not only under ideal circumstances, but also in clinical settings when deployed in under real-life routine conditions (Steckler & McLeroy, 2008). Therefore, the present study aimed to evaluate the accuracy and predictive value of the Empatica E4 wristband by comparing it to the VU-AMS as reference golden standard while worn on both wrists in a clinical population of adolescents in residential care.

METHODS

Participants

Data for this study were obtained from a feasibility study testing three game-based meditation interventions among adolescents in residential care (Schuurmans et al., 2020). This study yielded data of fifteen participants who wore two recording devices during two experimental testing sessions and twelve intervention sessions. During the experimental testing sessions and at the beginning of each intervention sessions, participants' baseline HRV parameters were measured. The intervention sessions also included at least two measurement moments of participants' heart rate parameters during short meditation sessions. For a detailed description of the study protocol see (Schuurmans et al., 2020). The sample consisted of fifteen adolescents (nine males, six females) with a mean age of 14.46 years (standard deviation [SD] = 2.40).

Sample size

We expected that the recordings of the two measurement devices would be strongly correlated with an effect size of at least .5 (Cohen, 1988). According to the sample size requirements for estimating ICCs proposed by Bonett (2002), this would require a sample size of at least 218 cases.

Although our sample did not consist of a large number of individual participants, the study did include multiple measurement days for each participant, as suggested by Bonett (2002). One experimental testing session was conducted before the start of the intervention and one after the intervention ended. During these experimental testing sessions, one recording was conducted. During the twelve intervention sessions, at least two recordings were conducted. Recordings that were retrieved during the sessions took three-to-five minutes. Data from one participant was excluded due to a high frequency of premature atrial complexes (PACs), a common arrhythmia which is considered a benign phenomenon that could impact assessments. Two participants dropped out because they refused to continue with the study. In total, 356 identical segments of NN intervals were recorded, which can be considered sufficient.

Procedure

The current validation study used different levels of validity assessment, as suggested by Van Lier and colleagues (2020). They identified three levels of validity assessment: (1) signal level: the most direct comparison that assesses the capability of a device to generate the same raw data as the reference device; (2) parameter level: whether a device produces physiological parameters (e.g., HR) for each individual similar to the reference device; and (3): event level: a comparison with the reference device on ability to significantly detect event(s) via group means. In the current study, the validity of the Empatica E4 was assessed on the signal level with intraclass correlations (ICCs), cross correlations (CCs) and parameter level with Bland Altman plots. For the current study, no data were available on the event level.

Ethical review and approval were provided by the CMO Arnhem-Nijmegen under protocol NL58674.091.16. Adolescents were recruited within three residential youth care institutions. All participants gave written informed assent and their legal guardians gave written consent. Participants were randomly assigned to one of three conditions: *Muse*, *Daydream*, or *Wild Divine Games*. Although the conditions consist of three different interventions, all make use of meditation-based relaxation techniques and short meditation sessions. Thus, data recordings of the three interventions were highly comparable, making these data suitable for validation of the Empatica E4 wristband. Participants received a 15 euro gift check at the end of the second experimental testing session.

Data recording

Recordings were conducted at the pre-test experimental sessions (week 1), the intervention sessions (week 2-7), and at the post-test experimental session (week 8). Participants wore two recording devices during all sessions: the Empatica E4 wristband (Empatica Inc., Cambridge, MA, USA; McCarthy et al., 2016; Ollander et al., 2017; van Lier et al., 2020) and the VU-AMS (Vrije Universiteit, Amsterdam, the Netherlands; De Geus et al., 1995; Willemsen et al., 1996). Baseline HRV parameters were obtained while participants watched an aquatic video. This is a common procedure to achieve a measurement of baseline recordings to which to compare the parameters retrieved during other conditions (Piferi et al., 2000). Participants were instructed to sit quietly and watch the aquatic video for four minutes. Halfway the intervention there were two participants who refused to continue with the VU-AMS recordings, due to discomfort with the electrodes that needed to be applicated and removed each session. These participants completed the remaining sessions without VU-AMS recordings.

Empatica E4

The Empatica E4 wristband contains four sensors: (1) an electrode for Electrodermal activity (EDA), (2) 3-axis accelerometer, (3) a temperature sensor, and (4) a photoplethysmography (PPG) to measure blood volume pulse (BVP) from which it derives HR and the inter beat interval (IBI) (Empatica, 2018; see Figure 1). Using the Empatica Manager, data were uploaded to Empatica Connect and raw CSV data were downloaded and analyzed using Kubios HRV 3.0 (Tarvainen et al., 2014). Kubios offers five artefact correction options based on very low to very high thresholds. We compared Empatica E4 recordings with all five Kubios artefact correction levels to the VU-AMS recordings and without any Kubios artefact correction. Recordings without post-hoc artefact correction showed the highest correlation, so no Kubios artefact correction was used for the analyses. This is not surprising, since the Empatica E4 already uses an algorithm that removes wrong IBIs (Empatica, 2018c).

VU-AMS

The VU-AMS is a lightweight ambulatory device that records the electrocardiogram and changes in thorax impedance from seven electrodes placed on participants' chest and back. Five electrodes are placed on the chest and two on the back. Participants need to partially undress (i.e., lift up their shirt) for placement of the electrodes. The electrodes are connected to a small device that can be worn unobtrusively underneath participants' clothes. Participants are able to perform their normal daily routines with little constraint in their movements. The ECG had a sampling rate of 1000 Hz and heart rate was obtained from the time between two adjacent R waves. For a detailed description of the VU-AMS assessment procedures see Vrije Universiteit (2015). Heart rate data were extracted and visually inspected for artefacts with the Data Analysis and Management Software (DAMS) program version 4.0.

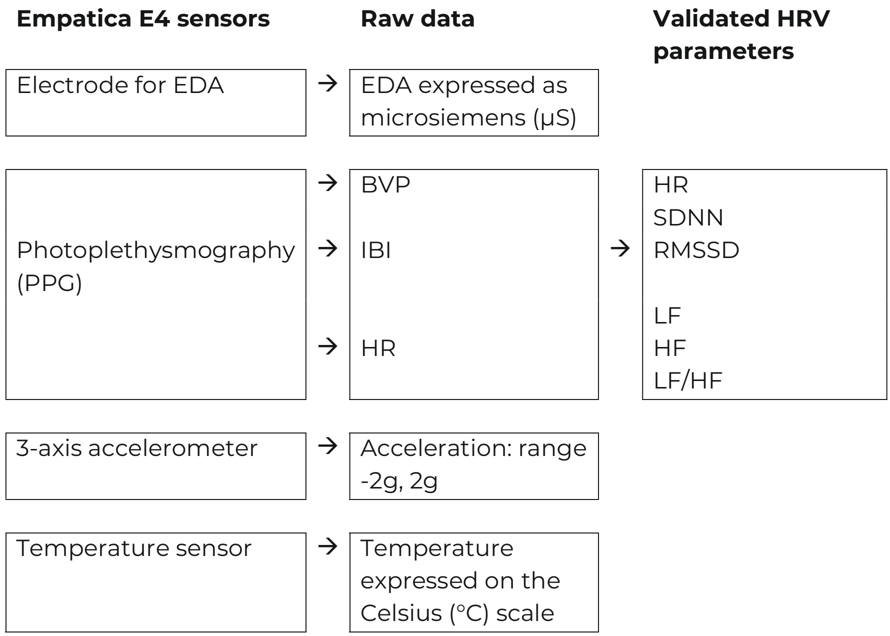

Figure 1. Block diagram for the Empatica E4 wristband

Note. BVP = blood volume pulse, EDA = electrodermal activity, HF = high frequency, HR = heart rate, IBI = inter beat interval, LF = low frequency, LF/HF = ratio between low and high frequency, RMSSD = root mean squared differences of successive difference of intervals, SDNN = standard deviation of the normal to normal interval.

Data analysis

Time domain analysis concerns the amount of HRV within the samples. To calculate HRV parameters for time-domain analysis, 343 identical segments of NN intervals were selected from the VU-AMS and E4 recordings. These metrics include:

- RR intervals (RR): the number of detected R waves in the ECG.
- mean HR: average time between two heart beats.
- SDNN: the standard deviation of the NN interval, based on normal sinus beats, thus abnormal beats (e.g., ectopic beats that originate outside the right artrium's sinoatrial node) are removed. SDNN tends to be higher when the LF band has more power compared to the HF band (Shaffer & Ginsberg, 2017).
- RMSSD: the root mean squared differences of successive difference of intervals, also based on normal sinus beats. RMSSD stands for HR beat-to-beat variance and is the main estimation for PNS mediated changes in HRV (Shaffer & Ginsberg, 2017).

Frequency-domain analysis allows for estimating sympathetic and parasympathetic contributions of HRV. To calculate HRV parameters for frequency-domain analysis, 243 identical segments of NN intervals were selected from the VU-AMS and E4 recordings (since frequency-domain analysis requires recordings of at least five minutes). Fast Fourier transformation allows for separating HRV into components of the power spectrum:

- Low frequency (LF) activity (0.04 to 0.15 Hz). When measured under resting conditions, like in the present study, it typically reflects baroreceptor activity, which helps to maintain blood pressure (Shaffer & Ginsberg, 2017)
- High frequency (HF) activity (0.15 to 0.40 Hz) reflects PNS activity and is highly correlated with RMSSD (Shaffer & Ginsberg, 2017). The ratio between low and high frequency power (LF/HF) is an estimation for the ratio between SNS and PNS activity. LF/HF might provide insight in the relative influence of the SNS and PNS, but there is debate on the relative relationship of both branches (Jarczok et al., 2013).

Statistical analysis: Accuracy

Descriptive statistics (mean and SD), intraclass correlation (ICC) and cross-correlations (CC) were calculated for all variables. Cross-correlations of > .80 were considered valid (van Lier et al., 2020). Normality was assessed by Kolmogorov-Smirnov tests. None of the variables were normally distributed (all $p < .05$). Mann-Whitney tests were used to detect differences between VU-AMS and E4 recordings. Effect size values (*r*) were calculated for the significantly different outcomes to determine the effect sizes (Cohen, 1988). Difference factors (DF%) were calculated to give a difference estimation in terms of percent $(X_{VU\text{-}AMS} – X_{E4}) / X_{VU\text{-}AMS}$ as was done by Ollander and colleagues (2017). Bland-Altman plots were constructed and 95% limits of agreement (LoA), where the true value varies, were calculated for all parameters (Bland & Altman, 1986). Bland-Altman plot analysis provides an evaluation for the bias between mean differences of two methods, and an estimation for an agreement interval wherein 95% of the differences of the second method fall, compared to the first.

Statistical analysis: Predictive validity

To evaluate predictive validity, it was assessed to what extent recordings provided by the Empatica E4 wristband led to the same conclusions as the VU-AMS. We conducted analyses to assess potential differences between the three game-based interventions. For each condition, Mann-Whitney tests were conducted to test whether ANS parameters that were recorded during meditation could be distinguished from those recorded during rest.

All analyses were conducted four times: with Empatica E4 recordings of the device worn on participants' left hand, worn on participants' right hand, worn on participants' dominant hand, and worn on participants' non-dominant hand. For parsimony, only data of the Empatica E4 recordings on participants' left hand are reported. Differences with the E4 recordings on the right hand, dominant hand, or non-dominant hand were minimal, not significant, and did not lead to different conclusions.

RESULTS

Accuracy

Bivariate correlations between ANS variables are presented in Table 1. Table 2 shows descriptive statistics, difference factors, LoA and outcomes of Mann-Whitney tests for ANS parameter recordings obtained from both the VU-AMS and the Empatica E4 during rest and mediation. Highly significant (all $p < .001$) and strong ICCs were observed for HR ($r = .99$), SDNN ($r = .91$), RMSSD ($r = .89$), and HF ($r = .88$). Medium yet significant ICCs were observed for RR ($r = .62$), LF ($r = .72$) and LF/HF ($r =. 73$). The difference factor for HR was particularly low with 1.60%. Differences for SDNN, LF, and HF were below 25%, those for RR, RMSSD, and LF/HF were higher than 25%. Notably, LoA were small for HR.

There was no difference between VU-AMS and Empatica E4 recordings for HR. For all other parameters, significant differences were found between the VU-AMS and Empatica E4 recordings, although effect sizes were small for SDNN, LF, and HF. Differences for RR, RMSSD, and LF/HF yielded medium effect sizes. For time domain parameters, the E4 estimates SDNN lower and RMSSD higher than the VU-AMS. All frequency domain parameters estimated by the E4 were lower compared to the VU-AMS.

Table 1. Bivariate outcomes between ANS variables.

	RR	HR	SDNN	RMSSD	LF	HF	LF/HF
RR	-						
HR	.15**	-					
SDNN	-.11**	-.58**	-				
RMSSD	-.24**	-.55**	.88**	-			
LF	.02	-.28**	.57**	.35**	-		
HF	-.03	-.41**	.76**	.83**	.00	-	
LF/HF	-.20**	.07	-.01	-.11**	-.08*	-.09*	-

Note. ANS = autonomic nervous system, SD = standard deviation, HR = heart rate, SDNN = standard deviation of the NN interval, RMSSD = root mean squared differences of successive difference of intervals, LF = low frequency, HF = high frequency, LF/HF = ratio between low and high frequency. * $p < .05$. ** $p < .01$.

Table 2. Signal comparison of ANS parameters obtained from VU-AMS and Empatica E4 recordings (N = 345)

	VU-AMS		Empatica E4								
	M	SD	M	SD	DF%	ICC	CC	LoA	*U*	*p*	ES
RR	345.05	163.53	213.97	147.14	37.99	.62*	.46	-129.88 to 399.69	29004.00	< .001	.46
HR	84.64	11.85	83.28	11.62	1.61	.99*	.60	-2.47 to 5.18	56856.00	.115	.06
SDNN	63.24	35.16	56.94	43.08	9.96	.91*	.44	-22.40 to 32.87	54150.00	.010	.10
RMSSD	49.99	45.75	66.28	43.08	32.59	.89*	.47	-58.06 to 23.24	36230.00	< .001	.35
LF	1556.82	2427.98	1299.13	1658.38	16.55	.72*	.32	-3089.23 to 3528.61	54306.50	.009	.10
HF	2126.21	4977.59	1674.06	2733.47	21.27	.88*	.33	-4998.61 to 5496.62	54865.00	.017	.09
LF/HF	3.40	4.90	1.53	1.94	55.13	.73*	.29	-5.71 to 9.62	28618.00	< .001	.46

Note. ANS = autonomic nervous system, CC = cross-correlation, DF% = difference factor %, ES = effect size: *r*, HF = high frequency, HR = heart rate, ICC = intraclass correlation, LF = low frequency, LF/HF = ratio between low and high frequency, LoA = Limits of Agreement, M = mean, RMSSD = root mean squared differences of successive difference of intervals, SD = standard deviation, SDNN = standard deviation of the NN interval, *U* = Mann-Whitney between groups effect size. * $p < .01$.

Figure 2A to 2D show Bland-Altman plots for combined VU-AMS and Empatica E4 recordings on the time-domain variables: (2A) RR; (2B) HR; (2C) SDNN; and (2D) RMSSD. Figure 3A to 3C shovw Bland-Altman plots for combined recordings on the frequency-domain variables: (3A) LF; (3B) HF; and (3C) LF/HF. The differences between and the average of the two measures are represented on the Y-axis and X-axis, respectively.

Predictive value

Table 3 shows the descriptive statistics for both resting and meditation ANS parameters per game (*Muse, Daydream, Wild Divine*). Separately for each game, Mann-Whitney tests were conducted to test whether there was a difference in HR, SDNN, RMSSD, LF, HF, and LF/HF between resting and meditation ANS parameters. Based on the significant differences, for all parameters but RMSSD, testing outcomes of Empatica E4 recordings led to the same conclusions as for testing outcomes of VU-AMS recordings.

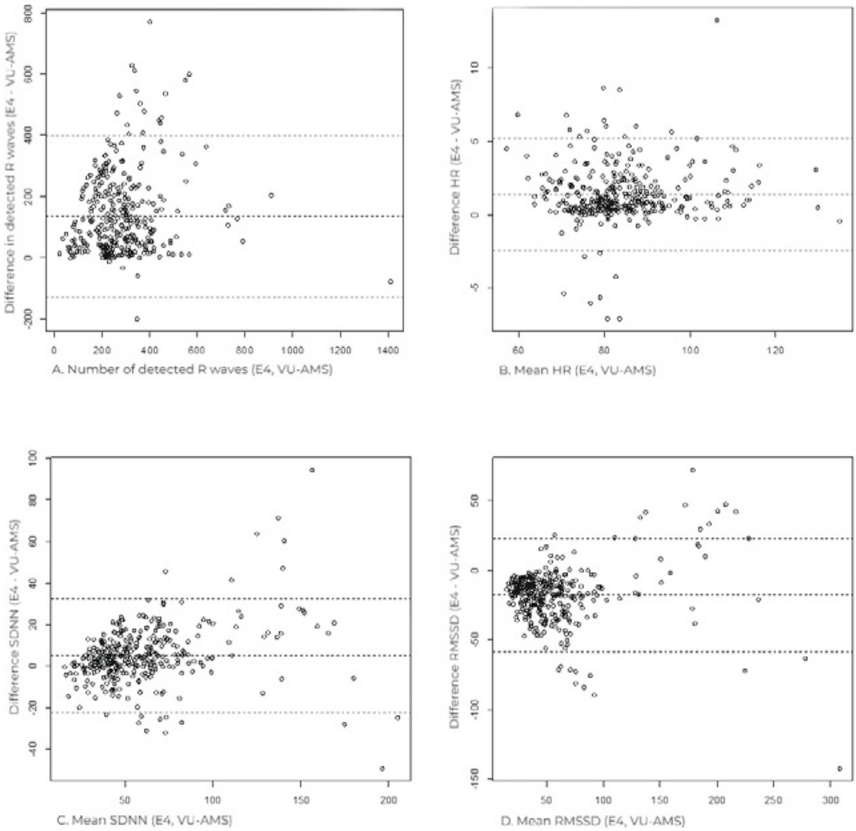

Figure 2A, 2B, 2C, and 2D. Bland Altman Plots for combined VU-AMS and Empatica E4 recordings on the time-domain variables.

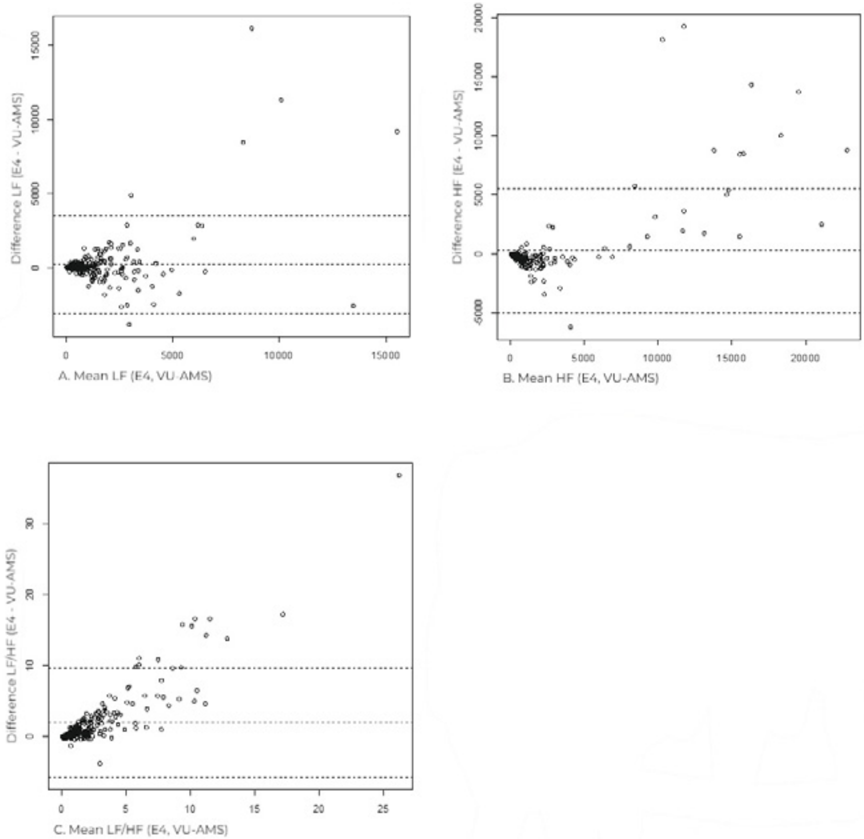

Figure 3A, 3B, and 3C. Bland Altman Plots for combined VU-AMS and Empatica E4 recordings on the time-domain variables.

Table 3. Differences between resting and meditation ANS parameters obtained from the VU-AMS and Empatica E4 per condition

	Baseline ANS				ANS during meditation				Testing for differences			
	VU-AMS		Empatica E4		VU-AMS		Empatica E4		VU-AMS		Empatica E4	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*U*	*p*	*U*	*p*
HR												
Muse	89.98	12.25	88.44	12.51	85.36	12.94	83.79	12.18	3449.00	< .001	3435.5	.002
Daydream	88.83	7.09	86.74	7.70	84.90	7.59	82.87	7.88	444.00	.012	423.50	.008
Wild Divine	77.50	9.50	75.92	9.93	75.73	7.43	75.28	8.30	595.00	.597	559.00	.995
SDNN												
Muse	49.45	18.49	45.85	17.03	49.37	15.34	46.68	13.53	4794.00	.881	4358.00	.420
Daydream	43.22	15.50	41.82	15.97	56.97	16.11	52.89	16.71	325.00	< .001	412.50	.007
Wild Divine	104.94	43.64	95.09	49.34	119.37	38.34	99.23	31.42	488.00	.086	445.50	.155
RMSSD												
*Muse**	29.54	15.97	54.09	23.82	37.27	19.19	54.69	22.74	3652.00	.001	4555.50	.756
*Daydream**	27.47	13.06	51.03	21.10	37.61	14.41	59.15	18.42	368.00	.001	506.00	.089
Wild Divine	110.55	74.30	121.88	84.30	109.25	62.25	105.71	56.59	638.00	.954	524.00	.662
LF												
Muse	915.34	889.27	802.51	766.86	821.87	684.10	760.74	722.40	1688.00	.986	4615.00	.838
Daydream	532.34	394.17	633.43	609.70	1254.81	1019.76	1392.24	1295.98	283.00	< .001	369.00	.001
Wild Divine	1695.82	889.49	1778.18	1124.74	5840.89	5071.62	4051.13	2945.14	506.00	< .001	253.00	< .001
HF												
Muse	345.65	405.47	663.57	613.32	581.32	599.53	919.47	867.93	1175.00	.005	3672.50	.010
Daydream	371.61	373.80	694.93	645.88	755.15	754.40	1172.21	980.27	367.00	.004	444.00	.016
Wild Divine	8259.74	9113.69	5093.93	5191.74	7051.98	7527.71	4792.88	4401.17	357.00	.569	547.00	.877
LF/HF												
Muse	5.63	7.28	1.74	1.82	3.08	4.03	1.42	1.71	1184.00	.006	3906.50	.049
Daydream	2.10	1.56	1.11	0.68	2.40	1.80	1.42	0.96	530.00	.328	561.00	.272
Wild Divine	0.69	0.68	0.60	0.51	3.75	4.30	2.68	3.69	234.00	.008	354.00	.008

Note. ANS = autonomic nervous system, SD = standard deviation, HR = heart rate, SDNN = standard deviation of the NN interval, RMSSD = root mean squared differences of successive difference of intervals, LF = low frequency, HF = high frequency, LF/HF = ratio between low and high frequency. * = different testing outcomes based on VU-AMS and Empatica E4 recordings.

DISCUSSION

Key findings

The present study was conducted to evaluate the accuracy and predictive value of the Empatica E4 wristband by comparing it to the gold standard VU-AMS in a clinical population of adolescents in residential care. As for accuracy, results show that Empatica E4 recordings of HR are highly comparable to VU-AMS recordings. For the other parameters, significant differences were found, although effect sizes were small for SDNN, LF, and HF. The Empatica E4 has good predictive value for all ANS parameters except for RMSSD. The statistical tests indicated that the results of the Empatica E4 and VU-AMS were comparable in distinguishing between resting and meditation.

The Empatica E4 performs excellent in estimating HR. Empatica uses two algorithms to detect heartbeats based on the blood volume pulse. Empatica (2019) states that their goal is to only detect beats of which they are certain. As a result of movement, pressure, or not wearing the device tight enough, the E4 fails to detect all beats resulting in data loss, and hence, misses the IBI on which the more complex calculations of HRV parameters are based. This loss of data resulted in the relatively large difference (37.5%) in RR detection between the Empatica E4 and the VU-AMS. This is comparable with other studies, for example, Van Lier and colleagues (2020) reported an artefact percentage of 45% in their data.

Yet, the results indicate that in situations where participants show minimal movement, as in our study, Empatica E4 recordings of HR and SDNN are highly accurate, although the Empatica E4 recordings are probably a slight underestimation of the real SDNN values (given that the VU-AMS provides higher, and presumably more accurate, values). Surprisingly, the RMSSD recordings, seem unreliable, since these not only differ substantially from the VU-AMS values, but also lead to different outcomes of statistical tests. Regarding the frequency-domain parameters, LF and HF perform most promising with minor differences from the VU-AMS recordings.

Comparison to other studies

Zheng and Poon (2016) and McCarthy and colleagues (2016) did not provide any parameters besides heart rate. Like Ollander and colleagues (2017), we calculated difference factors as an estimation of the difference between recordings of the two devices. Similar to their results, in our study difference factors for time domain parameters were very low for HR and higher for the time domain parameter RMSSD. Unfortunately, they did not report SDNN. Regarding the frequency domain parameters, our results for LF were comparable, but our DF% was lower for HF and higher for LF/HF. It should be noted that their sample was very small, so no strong inferences about their findings can be drawn.

Of all previous studies, Van Lier and colleagues (2020) provided the most extensive validation. Unfortunately, for time domain parameters, they only reported RMSSD and means and SDs for the RR intervals. Although they reported that data of the Empatica E4 can be considered valid for HR and RMSSD, we cannot make a comparison on SDNN, another value besides HR that we considered as very promising. Regarding validity on parameter level, our findings with respect to HR show – in line with findings of McCarthy and colleagues (2016), Ollander and colleagues (2017), Van Lier and colleagues (2020), and Zheng and Poon (2016) – that the Empatica E4 suited for estamating HR.

When we compare our results to the Polar validation studies of Giles and colleagues (2016) and Caminal and colleagues (2018), it can be noted that our correlations – although significant – are lower than the correlations of the Polar V800 and ECG recordings. These studies did not report mean HR, but for all other parameters, both time and frequency domain, the LoA reported in our study were wider. However, although these studies did use ECG to compare the Polar V800 to, these were not gold standard devices such as the VU-AMS or the Biopac.

Empatica E4 removal of artefacts

The PPG sensor of the Empatica E4 has LEDs that produce light oriented towards the skin. The light receiver measures the portion of the light that is reflected back. Therefore, the sensor requires direct contact with the skin and is sensitive to motion artefacts and incorrect placement (Allen, 2007; Y. L. Zheng et al., 2014). The Empatica E4 automatically removes these artefacts from the data, which results in shorter recordings. We found a difference score of approximately 40% in recording time between the VU-AMS and the Empatica E4, although there was minimal movement during the recordings and Empatica states that measurements in static condition could use IBI data as provided (Empatica, 2018c). The large amount of missing IBI data suggests that the Empatica E4 is highly sensitive to motion and motion artefacts, which impedes in particular its applicability for long-term recordings in daily life and experimental conditions that include exercise or movement. Artefacts in real-life situations are expected to have a significant influence on parameter estimation, which warrants further research on wearable, wrist-worn devices.

Strengths and limitations

Although four previous studies have provided a preliminary examination of the Empatica E4, this is, to our knowledge, the first study examining the validity of the Empatica E4 wristband while worn on both wrists and compared with a gold standard ECG device. The study was conducted with fifteen participants, but due to the repeated recording moment, our sample for time-domain analysis included 345 recording segments, which can be considered a valid sample size to validate ANS parameters (van Lier et al., 2020). Moreover, this study was conducted in a clinical population of adolescents in residential care and thus requires minimal translation to be relevant for clinical care. While posing substantial scientific challenges, research in clinical contexts is critical for practical innovation. We need to be aware of both the practical advantages and limitations of wearable HRV monitoring devices to decide whether these devices can be used in clinical care. For example, it should be noted that halfway the study, two participants refused to continue with the VU-AMS recordings due to discomfort, while they were willing to complete the remaining sessions wearing only the Empatica E4 wristbands. This illustrates the major practical advantage of wearable monitoring devices: wristbands do not require the application of electrodes and are non-intrusive, comfortable, and easy to wear.

To conduct the analyses for this study, we used data from a feasibility study that focused on measuring HR and HRV. While the Empatica E4 also measures EDA, XYZ raw acceleration, and skin temperature, the available data did not include these parameters. In particular EDA is a useful measure of sympathetic activation (Boucsein, 2012). We have to refrain from drawing strong conclusions regarding the validity of the Empatica E4 only based on its HR and HRV data. Future validation studies should include assessments of the other parameters provided by the Empatica E4, and possibly combine information from different parameters to see whether combinations could be even more informative. Also, our recordings were made under static conditions while participants were at rest. While informative as a first step toward validation of the Empatica E4, future research that include gold a standard reference device could focus on its ability to distinguish between states of stress and states of rest, and its recording quality when participants do not sit still. As our measurements did not include a stressor that was expected to prompt physiological changes, we were unable to assess validity on the event level.

In this validation study we used Kubios to process the Empatica E4 recordings, as recommended by Empatica (2018b). For the VU-AMS recordings, we used the DAMS program that was developed to analyze VU-AMS recordings (Vrije Universiteit, 2015). The reported differences between the Empatica E4 and VU-AMS recordings may – partly – be caused by software differences in processing and calculating HR and HRV parameters. In particular for frequency domain parameters, the use of different mathematical methods could lead to different results (Radespiel-Tröger & Rauh, 2003). It is noteworthy that in this study, the Empatica E4 performed worst on the frequency domain parameters. Although it is possible to analyze VU-AMS recordings in Kubios, we decided not to since this would deviate from the gold standard method that we wanted to compare the Empatica E4 to. Agreement between the two devices might have been higher when VU-AMS recordings were also analyzed with Kubios.

Conclusions

The development of wearable health technology provides new opportunities to measure HRV with easy-to-use devices such as the Empatica E4 wristband in clinical practice. Findings of the present study indicate that the Empatica E4 is practical and feasible for recording a limited set of ANS parameters. The strong correlations and agreement found between Empatica E4 and VU-AMS recordings for mean HR and SDNN suggest its potential as a valid tool for research on HR and HRV while people are at rest. While more research needs to be conducted, this study could be considered as a first step to support the use of HRV recordings provided by wearables.

Chapter 4

A novel approach to improve stress regulation among traumatized youth in residential care: Feasibility study testing three game-based meditation interventions

Published as

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ABSTRACT

Many youth in residential care suffer from posttraumatic symptoms that have adverse effects on a range of psychological, behavioural, and physiological outcomes. Although current evidence-based treatment options are effective, they have their limitations. Meditation interventions are an alternative to traditional trauma-focused treatment. This pilot study aimed to evaluate three game-based meditation interventions in a sample of traumatized youth in residential care.

Fifteen participants were randomly divided over three conditions (*Muse; DayDream; Wild Divine*) that all consisted of twelve 15-minute game-play sessions. Physiological measurements (heart rate variability) were conducted at baseline, post-treatment, and during each intervention session. Posttraumatic symptoms, stress, depression, anxiety, and aggression were assessed at baseline, posttreatment, and 1-month follow-up.

Physiological stress regulation was improved during the meditation sessions of all three interventions. User evaluations were in particular high for *Muse* with a rating of 8.42 out of 10 for game evaluation. Overall, outcomes on psychopathology demonstrated the most robust effect on stress. *Muse* performed best, with all participants showing reliable improvements (RCIs) in posttraumatic symptoms, stress, and anxiety. Participants who played *Daydream* or *Wild Divine* showed inconsistent progression: some participants improved, whereas others remained stable or even deteriorated based on their RCIs.

Preliminary findings show promising outcomes on physiology, psychopathology, and user evaluations. All indicate the potential of this innovative form of stress regulation intervention, and the potential of *Muse* in particular, although findings should be considered preliminary due to our small sample size. Further studies are warranted to assess intervention effectiveness effects of *Muse* or other game-based meditation interventions for traumatized youth.

INTRODUCTION

Youth in residential care have often been exposed to prolonged trauma, such as exposure to domestic violence, neglect, and emotional, physical, or sexual abuse. Specifically, over 90% of these youth have had traumatic experiences at a young age, of which the majority reports multiple events (Collin-Vézina et al., 2011). Posttraumatic symptoms of youth who suffer from chronic childhood trauma and do not receive appropriate treatment, are unlikely to decrease over time (Hiller et al., 2016), which makes effective intervention critical. Exposure to trauma increases the risk of psychological and behavioural problems (e.g., anxiety, depression, anger; (Collin-Vézina et al., 2011), extreme violence (Welfare & Hollin, 2012), repeated (sexual) victimization (Arata, 2006), health-risking sexual behaviour, delinquency (Smith et al., 2006), substance abuse (Bowen et al., 2017), and psychiatric disorders at a later age (Carr et al., 2013).

Traumatic experiences in early childhood not only have a devastating effect on youths' psychological development, but also on their physical health (Afari et al., 2014) and physiological stress systems (Beauchaine & Thayer, 2015; Otten et al., 2019). Stress activates the sympathetic nervous system (SNS), resulting in arousal (i.e., the fight-or-flight response; (Porges, 2011; Porges, 2007). The parasympathetic nervous system (PNS), however, is often referred to as the "brake" on sympathetic activity that reduces physiological arousal and promotes recovery after a stressor. Prolonged activation of the SNS results in dysregulation of the stress systems and subsequent stress regulation problems (Bremner & Vermetten, 2001; Corrigan et al., 2011; De Bellis, 2001). A key parameter of the PNS is cardiac vagal control, respiratory sinus arrhythmia (RSA; Porges, 2007, 2011). Higher RSA levels (i.e., more variability) are associated with improved abilities to regulate stress and emotional arousal (Graziano & Derefinko, 2013), whereas lower RSA levels are a clinical marker of stress sensitivity and predict posttraumatic stress and psychopathology after traumatic events (McLaughlin et al., 2015; Mikolajewski & Scheeringa, 2018; Skowron et al., 2011). Posttraumatic stress has been associated with abnormal neurobiological stress responses that are hypothesized to underlie behavioural, cognitive, and emotional problems (Bremner & Vermetten, 2001; De Bellis, 2001). Fortunately, these abnormalities can be normalized with treatment (Boyd et al., 2018).

Although evidence-based treatments such as trauma-focused cognitive behavioural therapy (TF-CBT) and eye movement desensitization and reprocessing (EMDR) have been found effective (Leenarts et al., 2013), there is considerable debate about whether trauma-focused treatment should start immediately after admission or whether the initial focus should be stabilization (Lindauer, 2015). TF-CGT and EMDR use exposure techniques that can evoke stress and be overwhelming for youth. When youth are unstable and lack the ability to regulate their emotions, arousal and anxiety may exacerbate posttraumatic symptoms and trigger self-destructive behaviour. Even when youth do exhibit the necessary skills in order for trauma therapy to succeed in promoting change, living in a residential institution provides a chaotic living environment that impedes therapeutic progress (Cohen et al., 2012). Also, youth are often difficult to engage in trauma treatment because they are still in denial or are not motivated to talk about their traumatic memories (Struik et al., 2017).

Given the difficulties often faced in traditional trauma treatment, other forms of intervention have gained popularity. A novel approach are meditation based interventions that can reduce posttraumatic symptoms without direct targeting (Boyd et al., 2018). Instead, the focus is on improving physiological stress regulation. Not only is there no need for youth to talk about their traumatic experiences, but also there are no intervention elements that specifically remind them to those events. Relaxation techniques (e.g., deep-breathing practices) increase a sense of control over the body and reduce psychological and physiological stress (Pascoe et al., 2017).

The present pilot study tested three *game-based* meditation interventions on their potential to improve youths' stress regulation. Game-based interventions are novel strategy to engage youth into treatment and hold advantages compared with traditional forms of therapy. These interventions do not rely on didactic learning but are able to tap into youth's intrinsic motivation (Granic et al., 2014). This is promising, as motivation is an important predictor of treatment effectiveness (Harder et al., 2012) and youth in residential institutions are usually characterized by a lack of motivation to change their behaviour (Van Binsbergen, 2003). Gamified treatment teaches youth techniques and skills, but with *less thinking* and *more doing* (Granic et al., 2014). This way of learning suits them better than memorizing certain principles (Vygotsky, 1978)—as conventional therapy does (Weisz & Kazdin, 2010). The repetitive nature of gameplay promotes long-term learning (Rosas et al., 2003) and thus may foster generalization of its effects to youth's daily lives.

The aim of the present pilot study was to evaluate the feasibility of three game-based meditation interventions for traumatized youth in residential care. To reach this goal, we assessed the interventions' potential to teach youth how to successfully regulate their physiological stress. We also assessed user satisfaction, and although this was not an effectiveness study, we aimed to show some preliminary effects on posttraumatic symptoms, stress, depression, anxiety, and aggression. Our ultimate purpose was to select the intervention that would best fit with our population for a large-scale randomized controlled trial (RCT).

METHODS

Participants

Participants were recruited within three open and secured residential youth care institutions for youth with and without intellectual disability (ID). Youth in residential institutions have complex emotional and behavioural problems. They are placed out of home and receive 24-hour care and mental health services. Inclusion criteria are (1) clinical levels of posttraumatic symptoms, measured as a score of 30 or higher on the Children's Revised Impact of Event Scale (CRIES-13;

Verlinden et al., 2014); (2) age between 10 and 18 years; (3) capable to comprehend and speak Dutch and (4) active informed assent to participate in the study from participants themselves and active consent from their legal guardians when participants are under the age of 16. Study participation was discussed with the participant's clinician before the researchers approached eligible participants. Participants who received current or recent (within the last 3 months) trauma treatment were excluded from study participation. There were no restrictions for other types of interventions that participants may receive. We will keep track of additional interventions and use it as a covariate in the analyses if necessary. There were also no restrictions regarding intellectual disability or psychiatric disorders as we wanted to obtain a sample that is representative for the population of youth in residential care.

Procedure

Ethical review and approval were provided by the CMO Arnhem-Nijmegen under protocol NL58674.091.16. Inclusion criteria consisted of a score of 30 or higher on the CRIES-13 (Verlinden et al., 2014). Exclusion criteria were severe psychotic symptoms and current or recent (within the last 3 months) EMDR or CBT treatment specifically targeting posttraumatic symptoms. Eligible participants were invited for an individual meeting with the researcher in which study procedures were explained. Legal guardians were sent an information form. All approached participants and their legal guardians gave active written consent. For a detailed overview see the flow diagram (Figure 1).

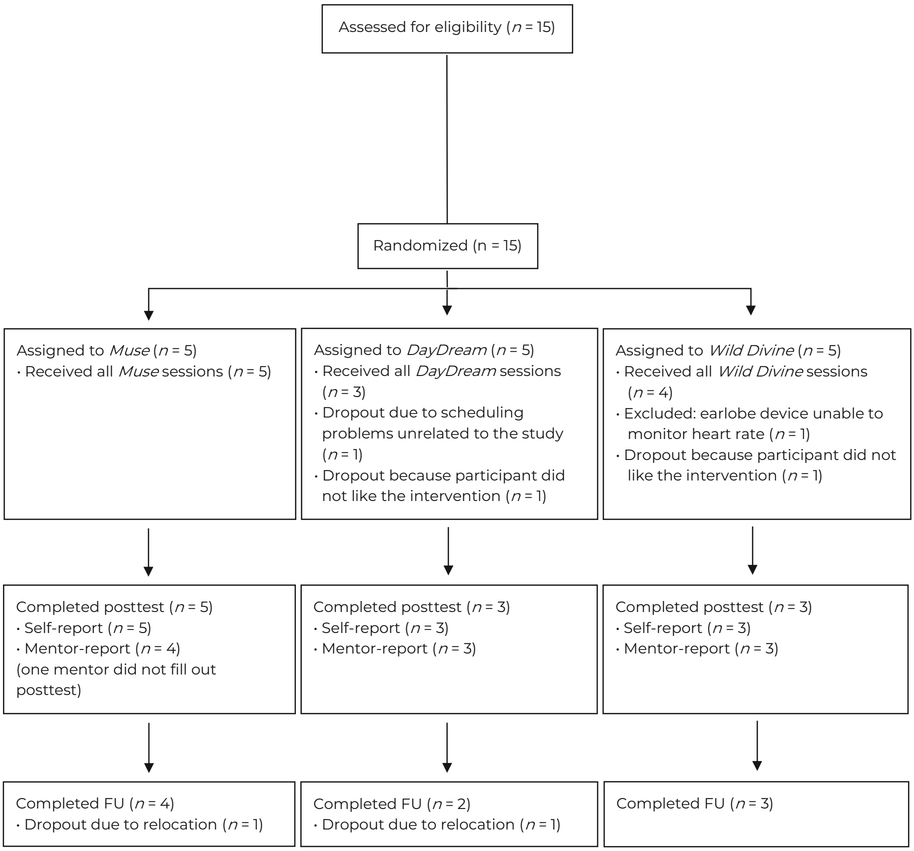

Figure 1. Flow diagram

Game-based interventions

The three tested interventions all make use of meditation-based relaxation techniques and either neurofeedback or biofeedback, three elements that independently have been found to normalize neurobiological abnormalities of individuals who suffer from posttraumatic stress (Boyd et al., 2018; Reiter et al., 2016; Schoenberg & David, 2014). All interventions consisted of twelve 15-minute sessions during which participants played the selected game. These sessions took place twice a week, for six consecutive weeks, and were led by the first author or a research assistant. Participants were randomly divided over the three intervention conditions in this study (see Figure 2 for game screenshots):

M*use* (developed by InteraXon, Toronto, Canada) is a meditation app that is played on an iPad. The 10 relaxation tutorials resemble elements of CBT (e.g., deep-breathing techniques; Weisz & Kazdin, 2010). Each tutorial is followed by a meditation session during which players are provided with neurofeedback on their arousal levels. The brain-sensing headband converts brain activity to gradations in the nature environment that is shown on the iPad. When the players' mind is calm, the environment shows calm and settled winds, but winds will pick up and blow when the players' mind becomes active.

DayDream (developed by Gainplay Studio, Utrecht, The Netherlands) is a meditative experience that incorporates neurofeedback with a MindWave headset. Players play on a laptop and when they start playing, they see a valley during wintertime. The basic principles of *DayDream* are similar to those of *Muse*, the seasons of the valley will transform according to brain activity. When players remain calm, they are able to change the season to spring and summer, and see animals wandering the valley.

W*ild Divine* (developed by Wild Divine, Las Vegas, Nevada) games are played on a laptop and consisted of the *Minigames of Wild Divine* and *Journey to the Eagle Mountain*. Both the *Minigames* and *Eagle Mountain* monitor the players' heart rate through biofeedback hardware (IomPE earlobe device). The *Minigames* are gamified relaxation tutorials that display a butterfly breathing cue to guide the player's breathing. *Eagle Mountain* is a serious game experienced through an eagle's viewpoint. The player flies free and has to catch wildlife. Breathing in coherence with the breathing cue increases success in the game: players will earn more points when they are calm. Each session, the player played one of the *Minigames*, followed by 10 minutes of *Eagle Mountain*.

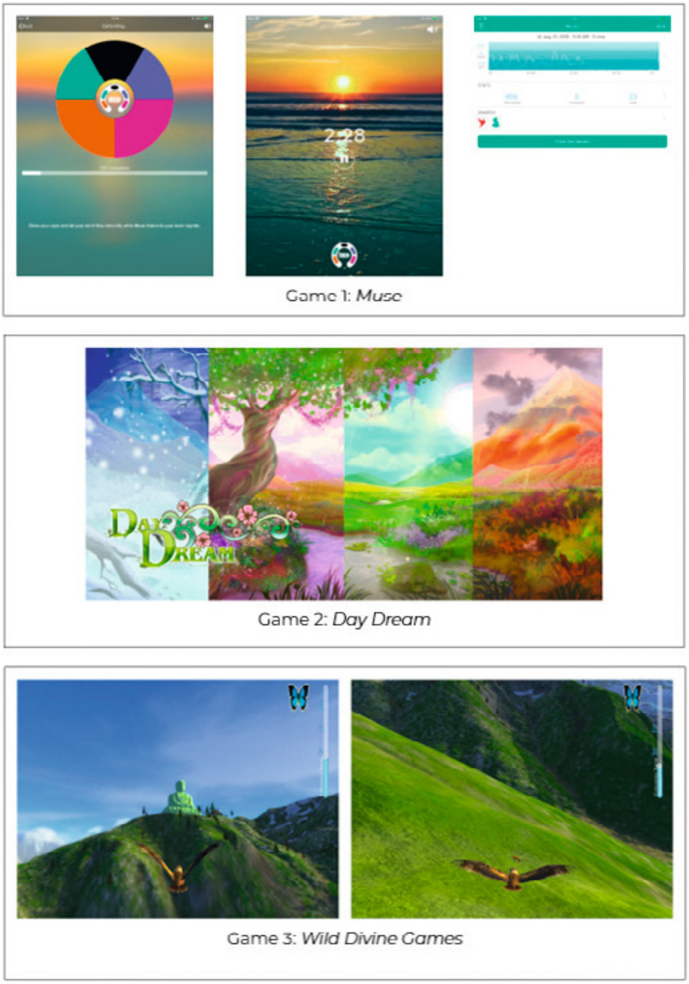

Figure 2. Screenshots of the three game-based interventions: *Muse*, *DayDream*, and *Wild Divine*.

Measurements

Primary outcome: physiology

Physiological recordings were conducted at baseline, post-treatment, and during each intervention session. To obtain autonomic nervous system (ANS) parameters, the VU University Monitoring System (VU-AMS) device was used (De Geus et al., 1995; Willemsen et al., 1996). At the beginning of each intervention session, participants watched an aquatic video for 4 minutes to get recordings of their resting ANS parameters to compare with the ANS parameters during the meditation sessions (Piferi et al., 2000).

Respiratory sinus arrhythmia. To measure physiological stress regulation, we derived RSA parameters with the VU-AMS device (De Geus et al., 1995; Willemsen et al., 1996). The VU-AMS is a lightweight ambulatory device that records the electrocardiogram and changes in thorax impedance from seven electrodes placed on participants' chest and back. For a detailed description of the VU-AMS assessment procedures see Vrije Universiteit Amsterdam (2015).

Secondary outcomes: questionnaires

Psychopathology measurements were conducted at baseline (self-report and mentor-report), posttreatment (self-report and mentor-reports), and at 1 month follow-up (self-report). The self-report measures were completed in an interview format to ensure comprehension, in particular, for participants with ID. The interviews took approximately 10 minutes and were conducted by the first author. Participants received a 15 euro gift cheque after the post-treatment measurement (they were informed about this gift check after they initially agreed to take part in the study).

User evaluations. Participants rated the items 'This is important for me', 'I liked today's session', and 'Satisfaction with the game' on a scale of 1 to 10.

Posttraumatic symptoms. Self-reported and mentor-reported posttraumatic stress were measured using the total scores of the CRIES-13 (Verlinden et al., 2013). This questionnaire has 13 four-point items that compose the subscales 'intrusion', 'avoidance', and 'hyperarousal'. The CRIES-13 has good reliability and validity (Verlinden et al., 2014).

D*epression, anxiety, and stress.* Self-reported depression, anxiety, and stress were examined with the subscale scores 'depression', 'anxiety', and 'stress' of the Depression Anxiety Stress Scales (DASS-21; (De Beurs et al., 2001; Lovibond & Lovibond, 1995). The DASS-21 consists of 21 four-point items. Reliability and validity of the DASS-21 are good, and internal consistency of the subscales is excellent (De Beurs et al., 2001).

A*ggression*. Self-reported aggression was measured with the Reactive Proactive Questionnaire (RPQ; Cima et al., 2013; Raine et al., 2006). This questionnaire consists of 23 three-point items and is composed of the subscales 'proactive aggression' and 'reactive aggression'. The RPQ has good reliability and validity for the total questionnaire, and both subscales have good internal consistency (Cima et al., 2013).

Analyses

All data are reported via descriptive statistics (mean and SD). The RSA data were positively skewed (skewness = 2.04, *SE* = .13, *p* < .01) and were log^{10} transformed to obtain normal distributions (Houtveen et al., 2002). To explore effects on RSA data that were measured each intervention session (in total, 355 segments of RSA recordings were used for this study), the non-parametric Wilcoxon Signed Rank test and a repeated measures mixed-model were conducted, controlling for clustering of data. Outcome data on psychopathology are based on the baseline and posttreatment measurements of the completers-only sample (*N* = 12). Due to our small sample size, we calculated Reliable Change Indexes (RCIs) as $(X_2-X_1)/SE_{diff}$ or $(X_{FU}-X_l/SE_{diff})$ (c.f., Zalta et al., 2016) to determine if any observed changes represented clinically significant change, as recommended by Jacobson and Truax (1991). Reliable change was determined with α set at 0.05 (two-tailed), which requires a 1.96 or -1.96 change in performance.

RESULTS

Participant demographics

The sample consisted of 15 adolescents (9 males, 6 females; mean age = 14.46, *SD* = 2.40) with clinical levels of posttraumatic symptoms. Nine participants were diagnosed with an ID. Average IQ scores were 86.69 (*SD* = 13.79) for the total sample, 94.00 (*SD* = 13.79), for participants without ID and 80.43 (*SD* = 14.73) for participants with ID. All participants were diagnosed with psychiatric disorders, most commonly reactive attachment disorder (n = 9), oppositional defiant disorder (n = 6), attention deficit disorder (n = 5), posttraumatic stress disorder (n = 4), and autism (n = 3). Comorbidity was high, with 11 participants (73.3%) diagnosed with at least two disorders. There was participant dropout at posttest (*n* = 4) and at follow-up (*n* = 6; see Figure 1 for more detailed information).

RSA

RSA outcomes are presented in Table 1. In all conditions, meditation RSA levels were higher compared to resting RSA levels, with medium to large effect sizes (Cohen, 1988). There was no difference between conditions in change in RSA levels (*F* [3, 101] = .27, *p* = .847).

Table 1. Physiological outcomes: RSA levels

	Resting RSA		RSA during meditation				
	Mean	SD	Mean	SD	z	p	r
Muse	1.65	.25	1.76	.18	-4.78	< .001	.61
Daydream	1.67	.20	1.81	.20	-3.67	< .001	.80
Wild Divine	2.23	.24	2.37	.13	-3.35	.001	.70

Abbreviation: RSA, respiratory sinus arrythmia

User evaluations

See Table 2 for user evaluations. *Muse* received the highest ratings on all outcomes, and in particular for "satisfaction with the game" with a rating of 8.42 out of 10, compared to a 7.07 and a 5.53 out of 10 for *Daydream* and *Wild Divine*, respectively.

Table 2. User evaluations

	Muse (n = 5)		DayDream (n = 3)		Wild Divine (n = 3)	
	Mean	SD	Mean	SD	Mean	SD
'This is important for me'	7.27	2.48	6.32	.85	6.35	1.99
'I liked today's session'	7.82	1.67	7.25	1.57	6.30	2.98
'Satisfaction with the game'	8.42	1.22	7.07	1.40	5.53	4.01

Psychopathology

Descriptive statistics on posttraumatic symptoms, depression, anxiety, stress, and aggression are shown in Table 3. Table 4 reports participant RCIs from baseline to posttreatment and from baseline to follow-up. Overall, outcomes on stress demonstrated the most robust results with 33.3-100% of participants showing reliable improvement and none of the participants showing reliable worsening. Among *Muse* participants, 100% showed reliable improvements in self-reported and mentor-reported posttraumatic symptoms, and self-reported anxiety and stress at posttreatment and follow-up. For depression and aggression, these rates ranged 40%-80%, other participants remained stable. Participants who played *Daydream* or *Wild Divine* showed inconsistent progression. Only one *Daydream* participant showed reliable improvement in posttraumatic symptoms, others remained stable. Stress and anxiety improvement rates ranged 33.3%-50%, other participants remained stable. For depression and aggression, improvement rates ranged 33.3%-100%, but there were also participants that deteriorated. Outcomes on posttraumatic symptoms for participants who played *Wild Divine* were inconsistent: although all participants themselves reported reliable improvement, their mentor-reports showed worsening of symptoms. Improvement rates for stress and aggression ranged 33.3%-66.7%, others remained stable. For anxiety, outcome changes were equally divided among improvement (33.3%), stability (33.3%), and decline (33.3%) and for depression, outcomes showed no reliable change at all.

Table 3. Outcomes on psychopathology: descriptive statistics

	Muse							
	Baseline		Posttreatment			Follow-up		
	Mean	SD	Mean	SD	*n*	Mean	SD	*n*
Posttraumatic symptoms								
Self-report	35.83	10.25	15.83	17.41	5	18.80	18.35	4
Mentor-report	32.84	14.46	20.00	10.07	4	-	-	-
Depression	7.17	4.45	3.33	4.08	5	2.80	4.66	4
Anxiety	7.17	2.93	3.00	2.83	5	4.00	5.34	4
Stress	10.21	3.74	5.83	5.12	5	4.20	6.53	4
Aggression	13.17	4.07	9.33	10.01	5	7.00	6.86	4
	DayDream							
	Baseline		Posttreatment			Follow-up		
	Mean	SD	Mean	SD	*n*	Mean	SD	*n*
Posttraumatic symptoms								
Self-report	39.67	17.39	36.33	13.05	3	25.00	12.72	2
Mentor-report	29.67	13.32	34.67	14.29	3	-	-	-
Depression	7.67	5.69	4.00	5.20	3	0.00	0.00	2
Anxiety	7.67	6.03	7.00	5.00	3	4.50	3.54	2
Stress	9.33	4.50	7.00	3.81	3	4.81	1.86	2
Aggression	13.00	4.36	10.67	6.81	3	6.50	3.54	2
	Wild Divine							
	Baseline		Posttreatment			Follow-up		
	Mean	SD	Mean	SD	*n*	Mean	SD	*n*
Posttraumatic symptoms								
Self-report	35.33	12.10	17.00	18.52	3	14.00	21.70	3
Mentor-report	29.76	7.67	32.63	11.81	3	-	-	-
Depression	5.00	7.81	4.67	8.08	3	5.33	8.39	3
Anxiety	4.33	5.13	5.00	7.81	3	5.00	6.93	3
Stress	7.00	6.13	4.38	7.58	3	4.67	8.09	3
Aggression	11.00	7.00	6.00	8.66	3	6.00	8.66	3

Table 4. RCIs for psychopathology outcomes: frequency and percentages

	Muse					
	Baseline to posttreatment (*n* = 5)			Baseline to follow-up (*n* = 4)		
	Decline *n* (%)	Stable *n* (%)	Improved *n* (%)	Decline *n* (%)	Stable *n* (%)	Improved *n* (%)
Posttraumatic symptoms						
Self-report			5 (100%)			4 (100%)
Mentor-report			4 (100%)			
Depression		3 (60%)	2 (40%)		1 (20%)	4 (80%)
Anxiety			5 (100%)			4 (100%)
Stress			5 (100%)			4 (100%)
Aggression		1 (20%)	4 (80%)		1 (25%)	3 (75%)
	DayDream					
	Baseline to posttreatment (*n* = 3)			Baseline to follow-up (*n* = 2)		
	Decline *n* (%)	Stable *n* (%)	Improved *n* (%)	Decline *n* (%)	Stable *n* (%)	Improved *n* (%)
Posttraumatic symptoms						
Self-report		2 (66.7%)	1 (33.3%)		1 (50%)	1 (50%)
Mentor-report		3 (100%)				
Depression	1 (33.3%)	1 (33.3%)	1 (33.3%)			2 (100%)
Anxiety		2 (66.7%)	1 (33.3%)		1 (50%)	1 (50%)
Stress		2 (66.7%)	1 (33.3%)		1 (50%)	1 (50%)
Aggression	1 (33.3%)	1 (33.3%)	1 (33.3%)		1 (50%)	1 (50%)
	Wild Divine					
	Baseline to posttreatment (*n* = 3)			Baseline to follow-up (*n* = 3)		
	Decline *n* (%)	Stable *n* (%)	Improved *n* (%)	Decline *n* (%)	Stable *n* (%)	Improved *n* (%)
Posttraumatic symptoms						
Self-report			3 (100%)			3 (100%)
Mentor-report	2 (66.7%)	1 (33.3%)				
Depression		3 (100%)			3 (100%)	
Anxiety	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)
Stress		2 (66.7%)	1 (33.3%)		2 (66.7%)	1 (33.3%)
Aggression		1 (33.3%)	2 (66.7%)		1 (33.3%)	2 (66.7%)

Note. RCI = Reliable Change Index.

DISCUSSION

This pilot study evaluated three game-based meditation interventions that all utilize biofeedback or neurofeedback to reinforce youth's stress regulation abilities. Notably, all three interventions were able to result in physiological improvement, measured as youth's RSA during meditation. This suggests that all interventions have potential for the treatment of traumatized youth in residential care. Although results should be considered explorative and as a first step to evaluate game-based meditation interventions for traumatized youth, initial outcomes are promising.

User evaluations regarding participants' perceived importance and enjoyment of the intervention sessions were most positive for *Muse*. User satisfaction with the game was high with an average rating of 8.42 out of 10 for game satisfaction and there were no dropouts. This indicates that this form of interventions forms a novel strategy to uniquely engage and intrinsically motivate youth (Granic et al., 2014). This is critical, since youths' motivation is a key predictor of treatment effectiveness (Harder et al., 2012) and youth in residential care usually lack treatment motivation (Van Binsbergen, 2003). In the other intervention conditions, two participants quit study participation because they did not like the intervention (*Daydream:* n = 1; *Wild Divine:* n = 1). These interventions also received lower ratings on game satisfaction than *Muse*.

Out of all psychopathology outcomes, improvements in experienced stress were the most robust across all conditions. This is not surprising, since the main goal of all three interventions was to improve stress regulation. *Muse* was the only intervention that resulted in reliable improvements in posttraumatic symptoms, stress, and anxiety for all participants. Although participants who played the other games also showed improvements on some outcomes, these were inconsistent: other outcomes remained stable or even showed deterioration. Surprisingly, the self-report outcomes on posttraumatic symptoms of participants who played *Wild Divine* showed reliable improvement, but their mentors reported worsening of symptoms. This inconsistency might be unrelated to the current study but due to the internalizing nature of many posttraumatic symptoms. As these problems tend to be inwardly focused and not direct observable, it might be possible that in some cases mentor-reports do not match with participants' own experience.

When we compared the three interventions, *Muse* was most positively evaluated and considered as the best fit for our high-risk, traumatized youth in residential care. Notably, none of the participants who played *Muse* dropped out. This suggests high acceptability, which is promising since attrition rates for traditional trauma-focused interventions range between 35% and 40% (Boyd et al., 2018).

Strengths and limitations

Traumatized youth in particular may fear facing their emotions and have feelings of distrust that interfere with their ability to fully engage in therapy (Cohen et al., 2012; Greenwald, 2006). The game-based meditation interventions in this study did not require youth to talk about their past. Youth are not confronted with traumatic memories nor with their emotions regarding these events. This makes these interventions particularly suitable as early trauma intervention when they are in need of treatment but lack stability or motivation for traditional trauma treatment.

This pilot study was conducted among traumatized youth in residential care. We did not hold on to commonly used exclusion criteria such as a minimal IQ-score, comorbid disorders, medication use, or other forms of treatment (other than trauma-focused treatment). Our sample thus reflects the real-world population of youth in our residential institutions and results require minimal translation for implementation in residential institutions. Another strength is the inclusion of varying behavioural measures, including more objective forms of experimental assessment as well as observational questionnaires, providing a basis to assess improvement in both therapy and real-life context. Also, our follow-up measurement was informative regarding potential long-term intervention effects.

We are aware that there are also limitations to this study. First, as mentioned before, with only 15 participants, our sample was very small. Of these 15 participants, 11 participants have completed the interventions they were assigned to. One participant had to be excluded because the IomPE earlobe device of *Wild Divine* was unable to monitor her heart rate. This might be due to her relatively small earlobes with three large earring holes. Another participant assigned to the *DayDream* condition had to quit study participation due to scheduling problems unrelated to the intervention and, as mentioned above, two participants quit study participation because they did not like the interventions.

Caution is warranted regarding any conclusions, in particular regarding the user evaluation and psychopathology outcomes, since post-test measures were only completed by participants who adhered to the protocol. Thus, for *DayDream* and *Wild Divine*, outcomes are probably overstatements of their real effects. However, as this was an explorative pilot study and not a superiority study that focuses on effectiveness outcomes, we decided to use completers-only data (Schumi & Wittes, 2011) to provide an indication of the true efficacy of the interventions when these are completed as planned.

Due to the lack of a control group, no comparison was possible with improvements over time due to general effects of youths stay in residential institutions. We thus cannot attribute causality to the quantitative data outcomes. Also, we registered but did not request participants to quit ongoing treatment and medication use for ethical concerns. However, there were no differences between the conditions (all $p > .70$). This study should be seen as an exploration of the needs of high-risk traumatized youth in residential care. Given the vulnerability of these youth and novelty of the interventions that are evaluated in this study, we aimed to provide a first indication of the feasibility of the interventions before conducting a large-scale RCT.

Implications and future directions

Game-based interventions are a novel approach to treatment that has received increased interest in the last decade (Lau et al., 2017). In residential care, two recent studies that evaluated a biofeedback videogame intervention showed high user satisfaction and reduced psychopathology outcomes (Schuurmans et al., 2015, 2018). A neurofeedback applied game intervention targeting anxiety was as effective as CGT (Schoneveld et al., 2018). Together with our findings, these all indicate the potential of game-based interventions for mental health care.

The interventions tested in the present study are a useful addition to traditional treatment programs. As the game-play sessions are executed according to a standardized protocol, these could be led by trained research assistants without requiring a clinician. However, we do not want to propose these forms of intervention as a stand-alone replacement for traditional therapy, but as a beneficial addition to current treatment programs. Although not tested in this study, it would be possible to let youth play these game-based interventions independently by themselves to help them regulate their stress.

This pilot study was a first explorative step to evaluate game-based meditation interventions for traumatized youth. A first next step would be to evaluate the effectiveness of these interventions in reducing posttraumatic stress and normalizing neurobiological abnormalities. We are currently conducting a RCT to test the effectiveness of Muse in reducing posttraumatic stress and normalizing neurobiological stress reactivity. Although this pilot study suggests the potential of *Muse*, only by running larger and more rigorous studies we can establish evidence of its effectiveness.

Conclusion

This pilot study shows the potential that game-based meditation interventions hold as alternative delivery models for the treatment of traumatized youth. Initial outcomes showed improvements in physiology, high user satisfaction, and improvements on posttraumatic symptoms, stress, and anxiety. Although findings should be considered preliminary due to our small sample size, this suggests that game-based meditation interventions form a new and engaging way to improve youths' posttraumatic stress. Further studies on this innovative form of intervention – and on *Muse* in particular – are warranted.

Chapter 5

Game-based meditation therapy to improve posttraumatic stress and neurobiological stress systems in traumatized adolescents: Protocol for a randomized controlled trial

Published as

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ABSTRACT

Many adolescents in residential care have been exposed to prolonged traumatic experiences such as violence, neglect, or abuse. Consequently, they suffer from posttraumatic stress. This not only negatively affects psychological and behavioral outcomes (e.g., increased anxiety, depression, and aggression), but also has adverse effects on physiological outcomes, in particular on their neurobiological stress systems. Although current evidence-based treatment options are effective, these have their limitations. An alternative to traditional trauma treatment are meditation-based interventions that focus on stress regulation and relaxation. *Muse* is a game-based meditation intervention that makes use of adolescents' intrinsic motivation. The neurofeedback element reinforces relaxation abilities. This paper describes the protocol for a randomized controlled trial to examine the effectiveness of *Muse* in reducing posttraumatic stress and normalizing neurobiological stress systems in a sample of traumatized adolescents in residential care.

This will be a multicenter, multi-informant, and multi-method randomized controlled trial. Participants will be adolescents (*N* = 80), aged 10 to 18 years, with clinical levels of posttraumatic symptoms, who are randomized to receive either the *Muse* therapy sessions and treatment as usual (experimental condition) or treatment as usual alone (control condition). Data will be collected at three measurement moments: pretest (T1), posttest (T2), and at two-month follow-up (FU). Primary outcomes are posttraumatic symptoms (self-report and mentor-report) and stress (self-report) at posttest. Secondary outcomes are neurobiological stress parameters under both resting and acute stress conditions, and anxiety, depression, and aggression at posttest. Secondary outcomes also include all measures at two-month follow-up: posttraumatic symptoms, stress, anxiety, depression aggression, and neurobiological resting parameters.

The medical-ethical committee Arnhem-Nijmegen (NL58674.091.16) approved the trial on November 15th, 2017. Participant enrollment started in January 2018 and the results of the study are expected to be published in the spring/summer of 2021. Study results will demonstrate whether game-based meditation therapy improves posttraumatic stress and neurobiological stress systems and is more effective than treatment as usual alone for traumatized adolescents.

BACKGROUND

Rates of chronic traumatic exposure among adolescents in residential care are staggering. Over 90% of these adolescents have been exposed to domestic violence, neglect, or emotional, physical, or sexual abuse at a young age (Collin-Vézina et al., 2011). Most of these traumatic experiences took place in the primary caregiving environment, even though caregiver support is essential for adolescents' attachment, resilience, and stress adaptation (Van der Kolk, 2005). Abuse by caregivers is probably the most interfering stressor that they can experience. Early traumatization interferes with adolescents' healthy development (Ellis & Del Giudice, 2019). It can have devastating effects on their psychosocial development (Van der Kolk, 2005), physical health (Afari et al., 2014), and neurobiological stress response systems (Bremner & Vermetten, 2001; Corrigan et al., 2011; De Bellis, 2001; Ellis & Del Giudice, 2019).

Neurobiological stress systems

Stress activates the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis to produce an appropriate stress response. The ANS consists of the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). Activation of the SNS occurs rapidly after stress exposure—usually within milliseconds to seconds. When confronted with a stressor, the SNS activates physiological processes frequently referred to as the 'fight or flight' response (Bauer et al., 2002). The effect of the SNS on cardiac activity can be indexed as pre-ejection period (PEP), which is the length of time between the contraction of the heart and the ejection of blood out of the heart into the aorta. A shorter interval would correspond with higher heart rate (HR), thus a decrease in PEP reflects an increase in SNS activity (Lozano et al., 2007). When the stressor disappears, the PNS inhibits sympathetic activation and facilitates bodily homeostasis (i.e., recovery and digestion) (Bauer et al., 2002). Generally, it has been assumed that the SNS and PNS are reciprocally coupled: when SNS activity increases, PNS activity decreases, and vice versa. However, various individual variations of ANS and PNS contributions to stress responses exist (Berntson et al., 1991; Berntson et al., 1994). One key parameter of the PNS is respiratory sinus arrhythmia (RSA), also referred to as vagal tone. RSA is a measure of heart rate variability that represents the parasympathetic nervous system control over heart rate and occurs at the frequency of respiration that facilitates adaptive responses to the environment (Porges, 1995; Porges, 2007). Lower RSA is associated with more internalizing and externalizing problems (Graziano & Derefinko, 2013) and may increase the risk on internalizing problems after trauma (McLaughlin et al., 2015; McLaughlin, Alves, et al., 2014).

The HPA axis has a slower response and longer duration than the SNS (Bauer et al., 2002; Gunnar & Quevedo, 2007). The primary effectors of the HPA axis system are glucocorticoids (steroid hormones). These have a slower onset and longer duration than the catecholamines of the SNS. Stress activates the paraventricular nucleus of the hypothalamus, which releases corticotropin-releasing hormone within a few minutes, usually peaking 15 minutes after the stressor (Herman et al., 2016). This stimulates the production of adrenocorticotropic hormone by the pituitary, which in turn signals the adrenal gland to release cortisol. Cortisol is also produced during non-stressful situations, referred to as basal cortisol (Gunnar & Quevedo, 2007). Research in adolescents on the impact of trauma on cortisol shows evidence for a link between trauma and HPA axis alterations but is characterized by the lack of a clear physiological profile. Exposure to trauma has been related to increased (Laceulle et al., 2017; Ouellet-Morin et al., 2019) and decreased cortisol levels (Busso et al., 2017; Laceulle et al., 2017; Ouellet-Morin et al., 2019).

In healthy individuals, the ANS and the HPA axis together generate adaptive responses in the face of acute threat. However, the experience of multiple, prolonged traumatic events can result in chronic activation of these stress systems, even when the original stressor has disappeared (Van der Kolk, 2005). The unpredictable and ongoing nature of the traumatic events, make these adolescents feel as if they are under constant threat of survival (Kliethermes et al., 2014). Unsurprisingly, the adverse effects of trauma become more severe and pervasive as the trauma lasts for a long period or the number of traumatic events increases (Cicchetti et al., 2001b; Collin-Vézina et al., 2011).

Trauma treatment

Although trauma-focused cognitive behavioral therapy (TF-CBT) and eye movement desensitization and reprocessing (EMDR) are well-established and effective treatments for traumatized adolescents (Leenarts et al., 2013), there are some inherent limitations. Both treatment models incorporate exposure techniques, verbal expression, and rely on the integration of cognition, emotion, and physiology. In order for the therapy to succeed in promoting change, sufficient capacity to regulate these systems is required. (Warner et al., 2013). Yet, traumatized adolescents often lack the capacity to control and regulate their impulses and emotions (Cook et al., 2005; Van der Kolk, 2005) and even when adolescents do exhibit the necessary skills in order for therapy to succeed in promoting change, residential care provides an often chaotic living environment that impedes the development of a therapeutic relationship and treatment progress (Cohen et al., 2012). Also, adolescents are often not motivated to talk about their experiences and re-experience their traumatic past (Struik et al., 2017).

Given the difficulties faced in traditional trauma treatment, alternative forms of intervention have gained popularity. The focus has shifted from mainly cognitive oriented and verbally dependent therapies to interventions that target physiological sensations. One promising approach is fostered by meditation interventions that focus on adolescents' stress regulation abilities. Meditation techniques (e.g., deep-breathing practices) focus on one's own bodily sensations and increase a sense of control over the body. Not only can feelings of stress be reduced and emotion-regulation capacities improved, individuals also showed beneficial changes in cardiovascular activity (Sarang & Telles, 2006; Streeter et al., 2012; Wu & Lo, 2008). Meditation can restore activity and connectivity in brain regions associated with posttraumatic symptoms (Boyd et al., 2018), lead to more balanced patterns of neurobiological stress responses (Pascoe et al., 2017) and modulate both HPA axis and ANS reactivity (Nguyen-Feng et al., 2019). Research on the effectiveness of meditation interventions for posttraumatic stress shows encouraging findings. Most studies have been conducted among adults (Boyd et al., 2018; Kim et al., 2013; Macy et al., 2018; Nguyen-Feng et al., 2019; Pascoe et al., 2017), but promising outcomes have been reported in traumatized adolescents too (Spinazzola et al., 2011a).

Game-based therapy

The current study aims to test the efficacy of game-based neurofeedback meditation therapy as an addition to treatment as usual (TAU) in a population of traumatized adolescents in residential care. Gaming forms a novel strategy to engage adolescents into treatment and holds several advantages compared to traditional therapy. Videogame or gamified interventions make use of adolescents' intrinsic motivation (Granic et al., 2014), while conventional treatment often depends upon imparting psychoeducational information, a didactic style of learning that contains few elements that are intrinsically motivating. Yet, motivation is an important predictor of treatment effectiveness (Harder et al., 2012) and adolescents in residential institutions are usually characterized by a lack of motivation to change their behavior (Van Binsbergen, 2003). Gamified treatment teaches adolescents techniques and skills, but with *less thinking* and *more doing* (Granic et al., 2014). This way of learning suits them better than memorizing certain principles (Vygotsky, 1978)—as conventional therapy does (J R Weisz & Kazdin, 2010). Game-play is characterized by its repetitive nature. Repetition promotes long-term learning (Rosas et al., 2003) and thus may foster generalization of its effects to adolescents' daily lives. There have been some studies conducted among adolescents in residential institutions that evaluated biofeedback videogame interventions. Results showed high user satisfaction, minimal attrition, and improved emotion-regulation (Kahn et al., 2009, 2013; Schuurmans et al., 2015, 2018).

Recently, the authors conducted a feasibility study that evaluated three game-based meditation interventions in traumatized adolescents in residential care (Schuurmans, Nijhof, et al., 2020). The interventions incorporated either bio- or neurofeedback and were assessed on their potential to improve physiological stress-regulation, user satisfaction, and preliminary effectiveness on posttraumatic symptoms, stress, depression, and aggression. The intervention that was evaluated positive on all outcomes and considered the best fit was *Muse*: a game-based neurofeedback meditation intervention.

Objectives

The primary aim of this study is to investigate the effectiveness of *Muse* as an addition to TAU in reducing posttraumatic symptoms (self- and mentor-report) and stress (self-report) compared with TAU in traumatized adolescents in residential care. We expect that playing *Muse* will result in a greater reduction of posttraumatic symptoms and stress than TAU alone.

As a secondary aim we will investigate the effectiveness of *Muse* on neurobiological stress systems under both resting and social stress conditions. It is hypothesized that participants who played *Muse* will show normalized neurobiological parameter compared to participants in the control condition. We will also assess the effects of playing *Muse* on anxiety (self-report), depression (self-report) and aggression (self- and mentor-report). It was expected that playing *Muse* would result in reduced anxiety, depression, and aggression.

METHODS

Study design

This study is a multicenter randomized controlled trial (RCT) with two parallel intervention groups. Outcomes will be compared at three measurement moments: before the intervention (T1), immediately after the intervention (T2), and at two-month follow-up (FU). Participants will be randomly assigned to the *Muse* or the TAU condition, stratified by gender and intellect to ensure equal ratios of participants in both conditions.

Study setting

Recruitment will take place in three residential institutions in The Netherlands that provide open and secured care for children and adolescents with and without intellectual disability. Residential care is the most intensive form of youth care and includes out-of-home placement and 24-hour care. These adolescents are unable to live at home due to severe psychiatric or behavioral problems, parental problems, or an unsafe home environment – often a combination of all of these. Adolescents live in group homes with group care workers as substitute care givers and receive treatment to target problem behavior. Residential care is often seen as a ‘last resort solution’ when there are no other options for treatment (Knorth et al., 2008).

Inclusion and exclusion criteria

Inclusion criteria are (1) clinical levels of posttraumatic symptoms, measured as a score of 30 or higher on the Children’s Revised Impact of Event Scale

(CRIES-13) (Verlinden et al., 2014); (2) age between 10 and 18 years; (3) capable to comprehend and speak Dutch; (4) active informed assent to participate in the study from participants themselves and active consent from legal guardians when participants are under the age of 16, obtained by the first author. Exclusion criteria are (1) negative clinician advice, for example when the participant already has other forms of treatment and the clinical fears that treatment burden would become too heavy (at this stage, participants are not randomized yet, so this exclusion criterium will affect both conditions equally); (2) simultaneous participation in another clinical intervention study; (3) acute psychotic symptoms; (4) current or recent (within the last three months) trauma treatment, specifically EMDR or TF-CBT specifically targeting posttraumatic symptoms. There are no restrictions for other types of interventions that participants may receive (e.g., medication, individual or group therapy). We will keep track of additional interventions and use it as a covariate in the analyses if necessary.

Recruitment

At adolescents' admission to the residential institutions that take part in the study, the CRIES-13 is included in the standard questionnaire battery that adolescents fill out at intake in these institutions. Adolescents with a clinical score of posttraumatic symptoms on the CRIES-13 (≥ 30), filled in less than three months before T1, will be considered eligible participants for this study. We will include adolescents with clinical levels of posttraumatic symptoms rather than adolescents who qualify for the diagnosis of 'posttraumatic stress disorder' (PTSD) because many adolescents who do not meet the criteria for PTSD, do suffer from posttraumatic symptoms and are in need of treatment (Griffin, 2012).

Additionally, clinicians will be asked whether the adolescent in question could be invited to take part in this study. After clinician consult, eligible participants will be contacted by the coordinating researcher who will explain the studies. We will obtain verbal and written assent from all participants, and when they are younger than the age of 16, also written consent from their legal guardians. Potential participants will be invited for an individual meeting with the coordinating researcher who will explain the study. Participants will be explicitly informed about the study design and that they can quit study participation at any moment without disadvantages. The researcher will also bring information letters with information on all aspects of the study. When adolescents initially agree to participate, they will be given the information letters. Two to three weeks later, they will be asked for their written assent and invited for the pretest measurement (T1).

Allocation and randomization

If all inclusion and no exclusion criteria are fulfilled, participants will be randomly assigned (1:1 ratio) to one of the two conditions using a randomization schedule that is generated by a Python script and stratified by gender, intellect, and residential institution. Allocation of conditions is not masked, but participants and their mentors will not be informed about the specific expectations regarding posttraumatic symptoms and neurobiological stress reactivity. We will explain that *Muse* is a relaxation app, designed to help participants deal with stress. Participant enrollment and assignment to the conditions will be performed by the first author.

Interventions

All included participants receive TAU: the treatment as recommended by their clinicians regardless of this study (e.g., individual/family therapy or medication. There are no restrictions for the type of interventions that participants can receive other than trauma-focused treatment, we only keep track of it. Participants in the *Muse* condition will receive the intervention sessions as an addition to TAU.

Muse is a game-based meditation application that is played on an iPad with a brain-sensing headband that utilizes real-time neurofeedback. The intervention takes six weeks and consists of two 15 to 20 minutes gameplay sessions per week. If participants are unable to make it to a session, this session will be rescheduled. All participants will complete twelve gameplay sessions in total. These sessions will take place in an office room located on the campus of the residential institution. *Muse* includes ten relaxation tutorials that resemble elements of TF-CBT such as deep-breathing techniques (Weisz & Kazdin, 2010). The tutorials are followed by three-minute meditation sessions. The meditation tutorials are in English, so we have created a standardized protocol with Dutch translations of each tutorial. The gameplay sessions will be supervised by research assistants who are trained to explain the tutorials according to this protocol.

Participants can choose the in-game environment that will be shown during the meditation sessions (e.g., beach, rainforest, city park). Before each tutorial, a short calibration will take place, during which the headband records the participants' brain activity during rest, as an up-to-date reference point for the upcoming meditation session. The tutorials are followed by three-minute meditation sessions. Participants will complete at least two tutorials and subsequent meditation sessions per intervention session. During the meditation sessions, participants hear sounds in the in-game environment that they have chosen previously. The brain-sensing headband provides real-time neurofeedback that is reflected by the intensity of activity in the environment. When participants' mind is calm, the environment shows calm and settled winds, but these winds will pick up and blow when participants' mind becomes more active. When participants succeed to remain in a calm state for a while, they will hear birds whistling. The neurofeedback element of the intervention involves retraining brain patterns through operant conditioning. Neurofeedback reinforces individuals' relaxation abilities (Price & Budzynski, 2009) and can reduce posttraumatic symptoms (Panisch & Hai, 2018).

After each meditation session, participants get feedback on their performance through a series of simple graphs. In order to motivate, *Muse* calculates points, provides awards, and sets goals and challenges to strive for. Performances are saved and tracked over time so participants can see their progress over time.

Study procedure

See Table 1 for an overview of all measurement moments and outcomes. The pretest (T1) will take place in week 1 and will include an interview, an aquatic video, a social stress task, and a hair cortisol measurement. During the interview, the self-report questionnaires will be administered. We will conduct interviews rather than let participants fill in the questionnaires themselves, to ensure cooperation and comprehension. The interview format is in particular suitable for adolescents with lower intelligence, since this lowers the bar to ask for additional explanation when they do not understand the question. Adolescents in residential care are often school dropouts and some of them may have trouble with reading, while they can easily answer the questions when these are read out aloud. The interviews will take approximately 30 minutes, with breaks in-between, and will be conducted by the coordinating researcher.

Participants will watch an aquatic video for five minutes (Piferi et al., 2000) to derive basal ANS parameters during rest, to compare to the ANS parameters derived during the stress task. The social stress task is an adapted and combined version of the Trier Social Stress Task for Children (TRIER-C) (Buske-Kirschbaum et al., 1997; Kirschbaum et al., 1993) and the Sing-a-Song Stress Test (SSST) (Brouwer & Hogervorst, 2014). Participants receive the introduction of a story and are told that they would have five minutes to compose the end of the story. Then, they will present their story for four minutes in front of a camera. Unlike the original TRIER-C, the judge panel will be replaced by a video camera (Popma et al., 2006). Participants will be recorded, allegedly for later assessment by a group of peers who will judge their performance. If the participant does not complete the four minutes for presenting, the researcher can use a standard set of prompts to encourage further narration. Immediately after the four minutes, participants will be asked to fill in a three-item manipulation check to rate how nervous the presentation task has made them on a scale from 1 (not nervous at all) to 10 (very nervous). Next, participants are given a booklet with song texts and are told that they have to sing a song in front of the camera. Participants have thirty seconds to choose a song and are expected to sing the song aloud for thirty seconds. Again, they will be asked to fill out the manipulation check immediately after the task. For an overview of the stress task, see Table 2. Participants will not be fully debriefed until they completed the second stress task at T2.

The posttest (T2) will take place in week 8 and includes, like the pretest (T1), an interview, aquatic video, social stress task, and a hair cortisol measurement. Since participants will be exposed to the social stress task twice, it is expected that they show habituation-related decreased levels of stress at T2 (Hoge et al., 2018; Schommer et al., 2003). To lower the risk for stress habituation and to improve methodological rigor for the second social stress task, participants will be given another story introduction that is comparable to the story that will be used for T1. At the end of T2, participants will be debriefed and told that the video recordings were deleted immediately after the measurement session.

The two-month follow-up (FU) will take place in week 16 and includes an interview, aquatic video, and a hair cortisol measurement. The FU measurement is conducted to provide additional information about potential long-term intervention effects. Therefore, we will use questionnaires and the parameters to measure neurobiological activity during rest that are relatively simple to obtain (i.e., a five-minute ANS measurement during the aquatic video and cutting the hair). Neurobiological reactivity requires the execution of a social stress task that is not only time-consuming, but eliciting stress among traumatized adolescents is not without risks and should only be done when essential for research purposes. For those reasons, neurobiological reactivity to acute stress was not included at FU.

Participants will receive a gift voucher of €15 at T1, a gift voucher of €10 and a stress ball at T2, and a gift voucher of €15 at FU. Participants' mentors (i.e., the group home worker with whom they have the most contact) will fill in the questionnaires in the same week as when the measurements with the participants are conducted.

Table 1. Overview of all measurement moments and outcomes.

		Procedure	Measures
T0	≤ 3 months before T1	Screening	*Questionnaire*
			Posttraumatic stress (CRIES-13)
T1	Week 1	Pretest measurement	*Questionnaires*
			Posttraumatic symptoms (CROPS & PROPS)
			Stress, depression, anxiety (DASS-21)
			Aggression (RPQ & PRPA)
			Neurobiological activity during rest
			Basal ANS activity
			Basal HPA axis activity
			Neurobiological reactivity to acute stress
			ANS reactivity
			HPA axis reactivity
	Week 2 – 7	Intervention	
T2	Week 8	Posttest measurement	*Questionnaires*
			Posttraumatic symptoms (CROPS & PROPS)
			Stress, depression, anxiety (DASS-21)
			Aggression (RPQ & PRPA)

Table 1. Continued

		Procedure	Measures
			Neurobiological activity during rest
			Basal ANS activity
			Basal HPA axis activity
			Neurobiological reactivity to acute stress
			ANS reactivity
			HPA axis reactivity
FU	Week 16	Two-month follow-up	*Questionnaires*
			Posttraumatic symptoms (CROPS & PROPS)
			Stress, depression, anxiety (DASS-21)
			Aggression (RPQ & PRPA)
			Neurobiological activity during rest
			Basal ANS activity
			Basal HPA axis activity

Note. CRIES-13: Children's Revised Impact of Event Scale; CROPS: Child Report of Posttraumatic Symptoms; DASS-21: Depression Anxiety Stress Scales; PROPS: Parent Report of Posttraumatic Symptoms; PRPA: Parent-rating scale for Reactive and Proactive Aggression; RPQ: Reactive and Proactive Aggression Questionnaire; ANS: autonomic nervous system; HPA: hypothalamic-pituitary-adrenal.

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Table 2. Overview of the social stress task.

	Timeline	ANS recordings	Cortisol samples
Before task			
-20 minutes			-20
-5 minutes	Aquatic video	Basal ANS parameters	
0 minutes			Pre
Start task	Anticipation speech task	ANS reactivity	
	Speech task	ANS reactivity	
	Manipulation check		
	Anticipation song task	ANS reactivity	
	Song task	ANS reactivity	
End task	Manipulation check		
After task			
0 minutes	Recovery	ANS recovery	Post
5 minutes			
10 minutes			+10
20 minutes			+20
40 minutes			+40

Note. ANS: autonomic nervous system.

Measures

Questionnaires

Screening instrument: the CRIES-13 (Verlinden et al., 2014) is a questionnaire with 13 four-point items to screen whether adolescents suffer from posttraumatic symptoms.

Posttraumatic symptoms and stress: Posttraumatic symptoms will be measured by participants' self-report as well as by mentor-report. The *Child Report of Posttraumatic Symptoms* (CROPS) (Greenwald & Rubin, 1999) is a self-report questionnaire that consists of 24 three-point items. The *Parent Report of Posttraumatic Symptoms* (PROPS) (Greenwald & Rubin, 1999) is a 30-item questionnaire that measures posttraumatic symptoms as reported by parents or other caretakers. In this study, participants' group home mentors will fill out the questionnaire. Several studies have demonstrated the validity and reliability of the CROPS and the PROPS in general populations (Greenwald et al., 2002). Additionally, the CROPS has been validated in a sample of juvenile offenders (Edner et al., 2017). The CROPS and the PROPS have been jointly developed so that the CROPS focuses on internal thoughts and feelings, whereas the PROPS focuses on observable behaviors.

Stress will be examined with the seven-item 'stress' subscale of the *Depression Anxiety Stress Scales* (DASS-21) (De Beurs et al., 2001; Lovibond & Lovibond, 1995). The DASS-21 is a self-report questionnaire that in total consists of 21 four-point items. Its validity and reliability are good and the subscales have an excellent internal consistency (De Beurs et al., 2001).

Anxiety, depression, and aggression: Anxiety will be measured with the seven-item 'anxiety' subscale of the DASS-21 (De Beurs et al., 2001; Lovibond & Lovibond, 1995).

Depression will be measured with the seven-item 'depression' subscale of the DASS-21 (De Beurs et al., 2001; Lovibond & Lovibond, 1995).

Aggression will be measured by participants self-report as well as by mentor-report. The *Reactive and Proactive Aggression Questionnaire* (RPQ) (Cima et al., 2013) is a self-report questionnaire that is composed of 23 three-point items. The RPQ consists of the subscales 'proactive aggression' and 'reactive aggression'. Its validity and reliability are good and both subscales have good internal consistency (Cima et al., 2013). The *Parent-rating scale for Reactive and Proactive Aggression* (PRPA) (Kempes et al., 2006) is a questionnaire that can be filled out by parents or other caretakers. The PRPA has eleven three-point items and consists of the subscales 'reactive aggression' and 'proactive aggression'. The PRPA total score and both its subscale scores have good validity (Kempes et al., 2006).

Neurobiological activity during rest

ANS parameters will be measured with the VU University Monitoring System (VU-AMS) (De Geus et al., 1995; Willemsen et al., 1996). This a lightweight ambulatory device that records the electrocardiogram and changes in thorax impedance.

Five electrodes are placed on participants' chest and two on the back. The electrocardiogram has a sampling rate of 1000 Hz and heart rate is obtained from the time between two adjacent R waves. Heart rate data will be extracted and visually inspected for artifacts with the Data Analysis and Management Software program version 4.0 (Vrije Universiteit, 2015). We will derive heart rate, RSA, PEP, respiration rate, and skin conductance parameters from the VU-AMS recordings.

Basal ANS activity: ANS parameters during rest will be derived from VU-AMS recordings while participants are watching an aquatic video for five minutes (Piferi et al., 2000).

Basal HPA axis activity: basal cortisol levels will be measured in participants' hair. Whereas saliva captures real-time cortisol levels that are subject to major fluctuations (van Ockenburg et al., 2015), hair cortisol provide a reliable way to assess average long-term activity of the HPA axis, thus cortisol exposure over longer time. Hair samples will be cut as close to the scalp as possible from a posterior vertex position. At least 15 mg of the most proximal 1.5 centimeter of each hair sample will be used for analysis – representing the basal level over the 6 weeks before the hair sample was taken. Hair processing and analyses will be conducted by the Laboratory of endocrinology of the Erasmus Medical Center, Rotterdam, the Netherlands. Hair samples will be washed in isopropanol and after solid phase extraction, hair cortisol will be quantified by liquid chromatography-tandem mass spectrometry (Noppe et al., 2015).

Neurobiological activity to acute stress

ANS reactivity to acute stress: ANS parameters will be measured while participants complete the social stress task (see Table 2). We will derive ANS parameters during the following segments of the stress task: (1) anticipation speech task, (2) performing speech task, (3) anticipation song task, (4) song task, and (5) recovery.

HPA axis reactivity to acute stress: Salivary cortisol levels will be measures before and after completion of the social stress task (see Table 2). Six saliva samples will be obtained with a collection device [Salivette, Sarstedt, Nümbrecht, Germany] twenty minutes (-20) and immediately (pre) before the social stress task, and immediately (post), ten (+10), twenty (+20), and forty (+40) minutes after the task (Table 2). Cortisol levels will be measured using the liquid chromatography-tandem mass spectrometry method with the Steriods Kit (Perkin Elmer, Turku, Finland).

Sample size calculation

Power calculation were performed using the program G*Power (Faul et al., 2007). An a priori power analysis for analysis of variance (ANOVA): repeated measures, within-between interaction was conducted. Based on previous meditation-based interventions for posttraumatic stress (Blanck et al., 2018; Boyd et al., 2018; Kim et al., 2013; Macy et al., 2018; Nguyen-Feng et al., 2019), we expected a small-to-medium effect size of d = .30 and a repeated measures correlation of .60.

To achieve a statistical power of at least .80, a sample size of 72 participants is required. We aim at including 80 participants in total to allow for 10% attrition, estimated from previous studies on game-based interventions in this population (Schuurmans et al., 2015, 2018; Schuurmans, Nijhof, et al., 2020).

Statistical analysis

To assess intervention efficacy, we will carry out repeated measures ANOVA analyses to detect differences in mean outcomes scores between the two conditions at T2 and FU. All analyses will be conducted in accordance with the intention-to-treat principle. Missing data will be imputed using the Markov Chain Monte Carlo [75]. Results will be expressed as differences in mean scores between the two conditions with 95% confidence intervals. P-values < 0.05 will be considered to indicate statistical significance.

Ethical and safety issues

Ethical review and approval of this study has been provided by the medical-ethical committee Arnhem-Nijmegen under protocol NL58674.091.16. All substantial amendments will be presented to the committee and competent authority. Before participants will be included in the study, they are informed about the study design, including randomization. We will explain participants that if they will be assigned to the control condition, they can play *Muse* after the follow-up measurement. Participants can end study participation at any time without consequences.

Privacy of participants will be protected by allocating identification numbers to the personal information that are traceable in a separate file, using double-key encryption. Data will be analyzed in a way that no conclusions can be drawn about individual participants. The three researchers that have access to the data of this study work at the residential institutions at which the study is conducted. Data entry will be double-checked to ensure accuracy. Biological material will be stored in a locked cabinet or a locked medical freezer at Pluryn until the end of the study. The material will be destroyed after laboratory analysis, as requested by the medical-ethical committee that approved the study.

Adverse events reported by participants or group care workers or observed by the researchers will be recorded and assessed in collaboration with participant's clinician. The potential relation with the intervention will be examined and participants will be followed until they have reached stability. Participation risk for this study is considered negligible, but if a participant seems negatively affected by the measurements or intervention, study participation will be discussed with the clinician and if necessary discontinued.

RESULTS

The current study was approved by the medical-ethical committee Arnhem-Nijmegen (NL58674.091.16) on November 15th, 2017. Participant enrollment started in January 2018. The results of the study will be published in international journals and presented on international conferences. Research findings are expected to be published in the spring/summer of 2021.

DISCUSSION

This study is the first to examine the effectiveness of a game-based meditation intervention in a clinical population of traumatized adolescents in residential care. To test the effectiveness of interventions within this population is crucial, since early alternations of these systems increase the risk of psychopathology at a later age (McLaughlin et al., 2010). At an early age, neurobiological stress systems contain high rates of plasticity (Pynoos et al., 2009), so adolescents could benefit substantially from effective treatment.

A particular strength of this study is that we use a multimodal, multi-informant approach with different types of assessment (i.e., questionnaires and physiological measures) and different informants (i.e., self-report and mentor-report). This type of approach is the most accurate way to assess and monitor adolescents mental health (De Los Reyes et al., 2015). Additionally, we will measure HPA axis and ANS reactivity, since both neurobiological stress systems are hypothesized to play a role in the development and maintenance of posttraumatic symptoms (Ellis & Del Giudice, 2019). To gain understanding in how trauma affects neurobiology, multisystem approaches need to be considered (Koss & Gunnar, 2018).

Limitations to the design of this study are the non-active control group, and because of that, the lack of condition concealment. Active control groups are more rigorous and leave no room for alternative explanations regarding attention, motivation, and behavioral expectation, but only when participants in both conditions have the same expectations of improvement (Boot et al., 2013). An optimal control group would require a game-based intervention that is comparable to *Muse*, but without its hypothesized working mechanisms. This is not feasible since this study will be conducted in residential institutions that have tight restrictions for casual gameplay. Clinicians do not agree on implementing a gameplay condition that is not expected to be beneficial for participants. The primary purpose of this study, however, is to test the effectiveness of *Muse* as an addition to TAU, not to determine its superiority to another form of treatment. Therefore, TAU can be considered as a valid control condition (Freedland et al., 2011). Due to the inactive control group, masking of conditions is not possible. Both participants and mentors will all be aware of the conditions that participants are assigned to. Thus, it might be possible that differential expectations will bias study outcomes.

Chapter 6

The effectiveness of game-based meditation therapy for traumatized adolescents in residential care: A randomized controlled trial

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ABSTRACT

Many adolescents in residential care have experienced traumatic events and suffer from posttraumatic stress. This study examined the effectiveness of *Muse*, a game-based meditation intervention, as an addition to treatment as usual (TAU) for traumatized adolescents in residential care.

Seventy-seven traumatized adolescents (10 – 18 years old) received either *Muse* and TAU (n = 37) or treatment as usual alone (n = 40). TAU consisted of evidence-based treatments that did not specifically target posttraumatic symptoms. Outcomes were measured at T1, T2, and two-months follow-up (FU). Primary outcomes were posttraumatic symptoms (self-report and mentor-report) and stress (self-report) at T2. Secondary outcomes included anxiety, depression, and aggression at T2, and all outcomes at follow-up.

The *Muse* group showed significantly greater improvements than the control group at T2 regarding self-reported posttraumatic symptoms, stress, anxiety, depression, and aggression. Mentor reports showed marginally significant decreases in posttraumatic stress at T2. There were no differences between the groups at FU, except for a marginally significant difference in self-reported posttraumatic symptoms, where the *Muse* participants showed larger decreases. As this study used a non-active control group, it only shows that *Muse* is a beneficial addition to TAU. It remains unclear which specific aspect of the intervention contributed to its effectiveness.

Game-based meditation therapy is a promising intervention that is more effective than treatment as usual alone. Implications of these findings for the role of game-based meditation interventions for traumatized adolescents in residential care are discussed.

INTRODUCTION

Over 90% of institutionalized adolescents have been exposed to traumatic experiences at a young age. These include domestic violence, neglect or sexual, physical, or emotional abuse, and these different types of traumatic events frequently co-occur (Collin-Vézina et al., 2011). Often, these events occur in the primary caregiving environment. Caregiver support is a key factor for adolescent attachment, resilience, and stress adaptation, and thus, trauma can have a profound impact on adolescent function, leading to posttraumatic symptoms, including nightmares, flashbacks, and an ongoing feeling of alertness and hypervigilance (Cook et al., 2005). These symptoms increase the risk of psychological and behavioral problems (e.g., anxiety, depression, anger), sexual risk behavior and victimization, and delinquency (Collin-Vézina et al., 2011; Smith et al., 2006). The traumatization is more severe and pervasive if the traumatic event lasts for a longer period and as the number of traumatic events cumulate (Collin-Vézina et al., 2011).

Adolescents with a mild intellectual disability (MID) are especially vulnerable to experiencing traumatic experiences (Mevissen & de Jongh, 2010; Reiter et al., 2007). Among all the adolescents in residential institutions, 20-25% are diagnosed with an MID (Van Nieuwenhuizen, 2010). Adolescents with a MID have problems with social functioning and have a lower IQ compared to their typically developing peers. This makes these adolescents more likely to experience traumatic events, in particular physical and sexual abuse (Reiter et al., 2007). They are also more vulnerable to the adverse effects of trauma, since they lack the ability to cope with traumatic events. In addition, their limited capacities complicate treatment effectiveness (Mevissen & de Jongh, 2010).

Despite the high prevalence of traumatized adolescents in residential care and the devastating effects of trauma on their development (Van der Kolk, 2005), trauma often goes untreated. Trauma-focused treatments, such as cognitive behavioral therapy (CBT) and eye movement desensitization and reprocessing (EMDR) are effective (Leenarts et al., 2013), but include exposure techniques and rely mostly on verbal expression and the regulation of cognition, emotions, and physiology (Warner et al., 2013). Yet, traumatized adolescents, and in particular those with an MID, often lack the capacity to control and regulate their impulses and emotions (Cook et al., 2005; Van der Kolk, 2005). Moreover, residential institutions tend to provide stressful living environments where instability, uncertainty, and a lack of trust impede the development of a therapeutic relationship and treatment progress (Cohen et al., 2012). Also, adolescents in residential institutions usually have had a substantial number of prior placements with concomitant therapies that did not work out for them (Baker & Curtis, 2006). As a result, the adolescents tend to doubt the value of therapy and are less motivated for future treatments (Greenwald, 2006). However, without the appropriate treatment, the adverse effects of the trauma are likely to continue over time (Hiller et al., 2016). Thus, this situation creates an evident need for additional or alternative forms of trauma treatments.

A novel approach that has recently gained popularity in the treatment of posttraumatic stress is mindfulness-based meditation intervention. Meditation-based approaches are thought to address emotional under- and overregulation, which are both core features of posttraumatic stress (e.g., hyperarousal or emotional numbing) (Boyd et al., 2018). There is little research on this topic among adolescents, but many studies among traumatized adults show reduced levels of posttraumatic stress and low dropout rates (Boyd et al., 2018). In addition, a recent feasibility study demonstrated the potential of a new innovative form of game-based meditation therapy (Schuurmans, Nijhof, et al., 2020). Therefore, in the present study, we aimed to test the effectiveness of *Muse*, which is a game-based meditation intervention, for traumatized adolescents in residential care.

Game-based interventions are a novel strategy to engage adolescents into treatment by making use of their intrinsic motivation to play games (Granic et al., 2014). Game-based bio- or neurofeedback interventions among adolescents in residential care reported improved emotion-regulation, high user satisfaction, and low attrition (Kahn et al., 2009, 2013; Schuurmans et al., 2015, 2018). These are promising results, because adolescents in residential care usually lack motivation for behavioral change (Van Binsbergen, 2003). which is a key predictor of treatment effectiveness (Harder et al., 2012). Moreover, learning by play a game suits adolescents better than didactic modes of learning (Vygotsky, 1978). which underlie most forms of traditional treatment (Weisz & Kazdin, 2010), and this is particularly true for those with an MID (Evmenova & Behrmann, 2011). The in-game environment offers the adolescents the opportunity to practice with acquired techniques, thereby promoting long-term learning and automatization into their daily lives (Rosas et al., 2003). The neurofeedback element of *Muse* provides the adolescents with real-time reports of their physical activity and rewards them each time they succeed in regulating their physical stress. This method of operant conditioning reinforces relaxation abilities and can reduce posttraumatic stress (Panisch & Hai, 2018).

The current study utilized a randomized controlled trial (RCT) to evaluate the effectiveness of *Muse* as an addition to treatment as usual (TAU) in traumatized adolescents with and without a MID in residential care. We predicted that playing *Muse*, as an addition to TAU, would result in a greater reduction of posttraumatic symptoms and stress compared to TAU alone (primary outcomes). We also hypothesized that playing *Muse* would lead to reduced anxiety, depression, and aggression, as well as improved executive functions (secondary outcomes).

METHODS

The trial was registered in the Netherlands Trial Register under ID NL6689; NTR6859. Pre-registered primary outcomes were posttraumatic symptoms (self- and mentor-report) and stress (self-report) at T2 (Schuurmans et al., 2020). Ethical review and approval were provided by the medical-ethical committee Arnhem-Nijmegen under protocol NL58674.091.16.

Design, setting, and procedure

The present study was a multicenter RCT that examined the effectiveness of *Muse* as an addition to TAU in reducing posttraumatic symptoms (self- and mentor-report) and stress (self-report), compared with TAU alone in traumatized adolescents in residential care.

We recruited participants from three residential institutions in The Netherlands that provide open and secured residential care for adolescents with and without MID. At admission to these institutions, the Children's Revised Impact of Event Scale (CRIES-13) (Verlinden et al., 2014) was administered and was used as a screening tool for adolescents with clinical levels of posttraumatic symptoms (score ≥ 30). We included participants based on clinically relevant symptoms rather than a diagnosis of post-traumatic stress disorder (PTSD) due to the underdiagnosis of PTSD (Miele & O'Brien, 2010). The inclusion criteria were as follows: (1) CRIES-13 score ≥ 30; (2) age 10 to 18 years; (3) being able to comprehend and speak Dutch; (4) active informed participant assent; and (5) active parental or legal guardian consent when the adolescents are under the age of 16. The exclusion criteria were as follows: (1) negative clinician advice, for example, when the participant already received other forms of treatment and the clinician feared that treatment burden would become too heavy (at this stage, the participants were not randomized yet, so this exclusion criterium equally affected both conditions); (2) simultaneous participation in another clinical intervention study; (3) acute psychotic symptoms; and (4) a current or recent (within the last three months) trauma treatment, specifically EMDR or CBT. There were no restrictions for concomitant interventions not targeting posttraumatic symptoms (e.g., medication, individual or group therapy). We kept track of the concomitant interventions and used these as covariates in the analyses.

The baseline measurement (T1) was conducted prior to the intervention (week 1). The posttreatment measurement (T2) was conducted immediately after the intervention (week 8). The follow-up measurement (FU) was conducted two months after the T2 (week 16). Participants received a gift voucher of €15 at T1, a gift voucher of €10 and a small stress ball as a present at T2, and a gift voucher of €15 at FU. The participants' mentors filled in the mentor-reported questionnaires during the same week that the participants' measurements were assessed.

Intervention

Muse. The participants in the *Muse* condition received the *Muse* intervention in addition to TAU. *Muse* is a game-based meditation application that is played on an iPad with a brain-sensing headband that utilizes neurofeedback. The intervention consisted of two 15-20 minutes gameplay sessions a week for six consecutive weeks. *Muse* includes ten relaxation tutorials that resemble elements of CBT (e.g., deep-breathing techniques) (Weisz & Kazdin, 2010). Each of the tutorials was followed by a three-minute meditation session. The gameplay sessions were supervised by research assistants who were trained to explain the tutorials according to the protocol. The participants completed at least two tutorials and two meditation sessions per intervention session. The brain-sensing headband provided real-time neurofeedback that was reflected by the intensity of the activity in the in-game environment that participants had selected previously (e.g., beach or rainforest). When participant's mind was calm, the environment showed calm and settled winds, but these winds picked up and blew when participant's mind became more active. After each meditation session, the participants received feedback on their performance in the form of points and awards. These were saved and tracked over time so that participants could see their progress. A more detailed description of the intervention can be found in the pilot study evaluating *Muse* (Schuurmans, Nijhof, et al., 2020).

Control condition. The participants in the control condition received TAU, which was the treatment as recommended by their clinicians, regardless of this study (e.g., medication, individual or group therapy). The types of TAU included a range of evidence-based interventions, except for trauma-focused treatments.

Measures

Posttraumatic symptoms were measured as reported by the participants' self-reports and as reported by their mentors. The *Child Report of Posttraumatic Symptoms* (CROPS) (Greenwald & Rubin, 1999) is a self-report questionnaire that consists of 24 items that rate symptoms on a three-point scale of intensity ('none', 'some', or 'lots'). The *Parent Report of Posttraumatic Symptoms* (PROPS) (Greenwald & Rubin, 1999) is a questionnaire with 32 three-point items that measures posttraumatic symptoms as reported by the parents or other caretakers. In this study, the participants' group home mentors filled out the questionnaire. The validity and reliability of both questionnaires was previously demonstrated (Greenwald et al., 2002).

Stress was examined using the seven-item 'stress' subscale from the *Depression Anxiety Stress Scales* (DASS-21) (De Beurs et al., 2001). The DASS-21 is a self-report questionnaire that consists of 21 four-point items that range from 'never' to 'almost always'. It has good validity and reliability, and the subscales have an excellent internal consistency (De Beurs et al., 2001).

Anxiety was measured using the seven-item 'anxiety' subscale from the DASS-21 (De Beurs et al., 2001).

Depression was measured using the seven-item 'depression' subscale from the DASS-21 (De Beurs et al., 2001).

Aggression was measured using the participants' self-report as well as the mentor-reports. The *Reactive and Proactive Aggression Questionnaire* (RPQ) (Cima et al., 2013) is a self-report questionnaire that is composed of 23 three-point items ranging from 'never' to 'often'. The RPQ consists of the subscales 'proactive aggression' and 'reactive aggression'. Its validity and reliability are good, and both subscales have a good internal consistency (Cima et al., 2013). The *Parent-rating scale for Reactive and Proactive Aggression* (PRPA) (Kempes et al., 2006) is a questionnaire that is filled out by parents or other caretakers. The PRPA has eleven three-point items ranging from 'never' to 'often' and consists of the subscales 'reactive aggression' and 'proactive aggression'. The PRPA total score and both its subscale scores have good validity (Kempes et al., 2006).

Motivation was assessed using the Intrinsic Motivation Inventory (IMI) (McAuley et al., 1988). The IMI consists of 37 seven-point items, including the following subscales: 'interest/enjoyment'; 'perceived competence'; 'pressure/tension'; 'value/usefulness'; 'perceived choice'; and 'effort'. The psychometric properties of the IMI show an adequate reliability and good validity (McAuley et al., 1988).

Randomization and masking

The participants were randomly allocated (1:1 ratio) into two conditions. The Python script randomization was executed by the first author and stratified by gender and MID (MID versus no MID) to ensure equal ratios in both conditions. The allocation of the conditions was not masked. It was not feasible to blind participants or mentors, but they were not informed about the specific hypotheses and were only told that *Muse* was designed to help participants cope with general stress.

Sample size calculation

The power calculation were performed using the program G*Power (Faul et al., 2007). An a priori power analysis for ANOVA: repeated measures, within-between interaction was conducted. Based on previous interventions for posttraumatic stress (Boyd et al., 2018; Kim et al., 2013; Panisch & Hai, 2018; Reiter et al., 2016), we expected a small-to-medium effect size of d = 0.30 and a repeated measures correlation of 0.60. To achieve a statistical power of at least 0.80, a sample size of 72 participants at T2 was required. We aimed at including 80 participants in total to allow for 10% attrition, as estimated from previous studies evaluating game-based interventions in this population (Schuurmans et al., 2015, 2018; Schuurmans, Nijhof, et al., 2020).

Statistical analyses

Our primary outcomes were immediate intervention effects on posttraumatic symptoms (self- and mentor-report), stress (self-report), and a clinical change in posttraumatic symptoms (self-report) at T2. The secondary outcomes were the long-term intervention effects on posttraumatic symptoms (self- and mentor-report) and stress (self-report) at FU and the immediate and long-term intervention effects on anxiety (self-report), depression (self-report), aggression (self- and mentor-report), and executive functions (mentor-report) at T2 and FU.

The outcome data were missing for 5% of the self-reports and 14% of the mentor-reports at T2 and for 35% of the self-reports and 36% of the mentor-reports at FU. A logistic regression analyses indicated that the data were missing at random. The missing data were imputed using full information maximum likelihood estimation for Markov Chains (Graham, 2009) Both intention-to-treat analyses and completers-only analyses were conducted.

We calculated the descriptive statistics for the participants' demographic and clinical characteristics. To assess potential differences between the conditions at baseline, t-tests and chi square tests were conducted. To examine the intervention effect on our main outcome variables, we used a mixed-model repeated measures analysis of variance with time as within-groups factor and condition as between-groups factor. The analyses were conducted comparing the change from T1 to T2 and from T1 to two-months FU. In order to estimate the effect size, the partial eta squared ($\eta 2p$) was derived. Covariates included age, gender, IQ, type of residential care (open versus secured), medication use, and concomitant therapy.

The analyses showed a significant interaction between gender and intervention effectiveness. We conducted additional mixed-model analyses to evaluate gender as a potential moderator of the intervention effect on self-reported posttraumatic symptoms. This exploratory analysis was conducted among the participants in the intervention condition and included gender (male; female) and the baseline posttraumatic symptoms (low: ≤ 23; medium: 24-32; or high: ≥ 33). We included baseline scores to check whether it was gender that moderated the intervention effect or the differences in the baseline levels of the posttraumatic symptoms, since the females reported higher levels of posttraumatic symptoms compared to the males ($p = 0.036$).

RESULTS

The recruitment of the participants took place between January 2018 and July 2019. Table 1 shows the demographic and clinical characteristics of the subjects. There were no significant differences at T1 between the two conditions based on the demographic or psychopathology variables.

As shown in Figure 1, 82 participants were enrolled in this study, of which 5 were transferred to another institution before the randomization, resulting in a sample size of 77 at baseline. Of these 77 participants, 73 (94.81%) completed the assigned intervention (TAU + *Muse* or TAU alone) and the T2 measurement. The two-months FU measurement was completed by 50 participants (64.94%).

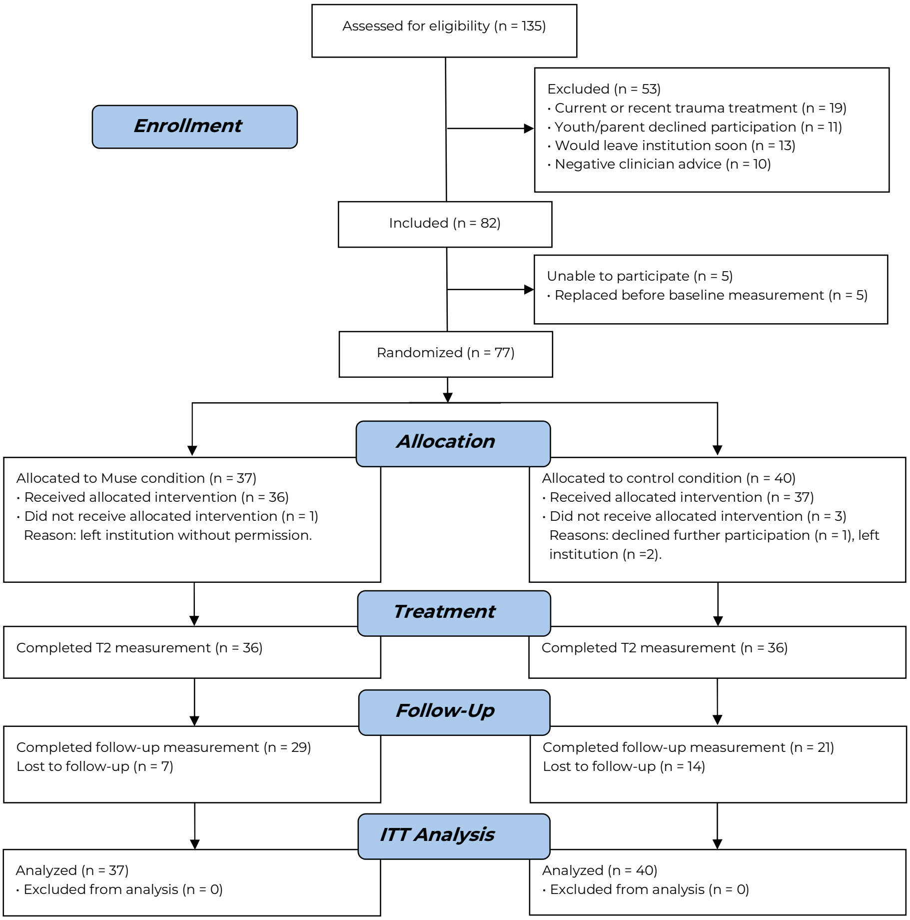

Figure 1. CONSORT Diagram illustrating the flow of the participants through the study.

Table 1. Demographic and diagnostic characteristics at baseline.

	Muse (n =38)		Control (n =39)	
Age (y), mean (SD)	14.93	2.63	15.31	1.91
Diagnosed ID, *n* (%)	16	42.11%	16	41.03%
IQ, mean (SD)				
Total sample	85.24	18.80	87.73	16.71
Sample no diagnosed ID	97.13	16.84	99.15	13.14
Subsample diagnosed ID	72.50	10.85	76.31	11.25
Gender, *n* (%)				
Male	23	60.53%	22	56.41%
Female	14	36.84%	16	41.03%
Transitioning			1	2.56%
Medication use	22	57.89%	19	48.72%
Concomitant therapy				
Animal assisted (e.g., dog, horse)	8	21.05%	5	12.82%
Creative (e.g., music, art)	4	10.53%	5	12.82%
Psychomotor therapy	7	18.42%	4	10.26%
CBT	4	10.53%	5	12.82%
Other individual therapy (e.g., emotion regulation/schema therapy)	4	10.53%	6	15.38%
Group therapy (e.g., resilience training)	1	2.63%	2	5.13%
Trauma- and stressor-related disorders				
PTSD	12	34.29%	10	28.57%
Reactive attachment disorder	14	40.00%	18	51.43%
Disinhibited social engagement disorder	0	0.00%	2	5.71%
ADHD/ADD	18	51.43%	21	60.00%
Neurodevelopmental disorders other than ADHD/ADD	4	11.43%	3	8.57%
Anxiety disorders	1	2.86%	1	2.86%
Autism spectrum disorders	13	37.14%	11	31.43%
Depressive disorders	2	5.71%	4	11.43%
Disruptive, impulse-control, and conduct disorders	12	34.29%	11	31.43%
Dissociative disorders	0	0.00%	1	2.86%
Obsessive-compulsive and related disorders	0	0.00%	1	2.86%
Comorbidity (>1 diagnosis)	25	71.43%	27	77.14%

Note. ADHD: attention-deficit/hyperactivity disorder, ADD: attention-deficit disorder, CBT: cognitive-behavioral therapy, ID: intellectual disability, PTSD: posttraumatic stress disorder, SD: standard deviation. One participant in the control condition was in an early stage of the transitioning process from male to female. This participant was excluded in the gender interaction analyses. The data regarding the participants' diagnoses were retrieved from the file analysis. For 7 participants (Muse: *n* = 3, controls: *n* = 4), these data were missing. The percentages refer to the subjects who had complete diagnosis data.

Primary outcomes

Table 2 shows the means and standard deviations for all the outcome variables per condition and the statistics of all the outcome analyses. Immediately after the intervention, the participants in the *Muse* condition reported lower levels of posttraumatic symptoms ($p < 0.001$) and stress ($p = 0.027$) compared to the participants in the control condition. The decrease in posttraumatic symptoms, as reported by their mentors, was marginally significant ($p = 0.074$).

Secondary outcomes

For all the self-reported secondary outcomes, we found a significant intervention effect at T2. The participants who played *Muse* reported decreased anxiety ($p = 0.004$), depression ($p = 0.004$), reactive aggression ($p = 0.039$), and proactive aggression ($p = 0.012$) compared to the participants in the control condition. None of the mentor-reported secondary outcomes, including aggression and executive functions, showed a significant intervention effect (See Table 2).

*T*he long-term intervention effect on self-reported posttraumatic symptoms was marginally significant ($p = 0.052$) at FU. The effects on other outcomes were not maintained after two months (See Table 2).

Table 2. Psychopathological outcomes at baseline, posttreatment, and two-month follow-up

	Descriptives				Statistical outcomes		
	Muse		Control condition				
	Mean	SD	Mean	SD	*F (df)*	*p*	η2p
Baseline (T1)							
Posttraumatic symptoms (SR)	26.03	9.74	23.92	9.87			
Stress (SR)	9.10	4.81	8.75	4.66			
Anxiety (SR)	6.25	4.11	5.30	3.28			
Depression (SR)	6.49	5.58	5.50	4.51			
Reactive agression (SR)	12.05	4.70	11.83	4.21			
Proactive agression (SR)	4.51	5.28	3.50	3.39			
Posttraumatic symptoms (MR)	27.58	9.76	26.08	10.52			
Reactive agression (MR)	3.14	2.65	3.33	2.53			
Proactive agression (MR)	6.97	3.91	6.40	2.92			
Executive functions (MR)	63.88	26.68	60.09	28.69			
Posttreatment (T2)							
Posttraumatic symptoms (SR)	19.40	10.64	24.54	8.85	21.64 (1, 75)	< .001	.22
Stress (SR)	6.61	4.41	8.21	4.57	5.00 (1, 75)	.027	.06
Anxiety (SR)	4.14	4.38	5.61	9.18	9.18 (1, 75)	.004	.11
Depression (SR)	4.42	3.98	5.87	5.19	9.01 (1, 75)	.004	.11
Reactive agression (SR)	8.17	5.02	10.05	3.91	4.49 (1, 75)	.039	.06
Proactive agression (SR)	2.07	2.96	3.56	4.58	6.78 (1, 75)	.012	.08
Posttraumatic symptoms (MR)	24.85	9.39	27.43	10.05	3.30 (1, 75)	.074	.04

Table 2. Continued

	Descriptives				Statistical outcomes		
	Muse		Control condition				
	Mean	SD	Mean	SD	*F (df)*	*p*	η2p
Reactive agression (MR)	3.61	2.70	3.84	2.68	.030 (1, 75)	.885	.00
Proactive agression (MR)	6.83	3.10	6.82	3.12	1.24 (1, 75)	.290	.02
Executive functions (MR)	63.24	27.68	63.40	30.41	.42 (1, 75)	.522	.01
Follow-up (FU)							
Posttraumatic symptoms (SR)	18.57	7.53	20.54	7.76	6.18 (1, 75)	.052	.07
Stress (SR)	6.63	4.31	7.22	3.40	.80 (1, 75)	.401	.01
Anxiety (SR)	3.97	3.83	4.34	2.58	2.57 (1, 75)	.151	.03
Depression (SR)	3.55	4.48	4.10	3.13	1.88 (1, 75)	.189	.02
Reactive agression (SR)	7.69	4.49	8.85	3.33	1.70 (1, 75)	.240	02
Proactive agression (SR)	2.07	2.96	3.56	4.58	6.76 (1, 75)	.183	.03
Posttraumatic symptoms (MR)	24.03	8.32	24.44	8.45	1.08 (1, 75)	.329	.01
Reactive agression (MR)	3.54	2.60	3.67	2.45	.16 (1, 75)	.709	.00
Proactive agression (MR)	6.73	3.14	6.96	2.73	1.97 (1, 75)	.183	.03
Executive functions (MR)	63.01	21.50	61.56	21.65	.17 (1, 75)	.687	.00

Note. MR = mentor-report, SR = self-report. The completers-only analyses showed minimal differences and led to the same statistical outcomes.

Exploratory analyses

No significant interaction between gender and baseline level of posttraumatic symptoms was found (p = 0.510). The main effects of both gender (F = 5.26 (1, 28), p = 030, η2p = .16) and baseline posttraumatic symptoms (F = 6.38 (1, 28), p = 005, η2p = .31) were significant (See Table 2). Specifically, although both groups experienced significant symptom reduction, the intervention effect was stronger for males than for females. Also, a stronger effect was found for the participants who reported higher levels of posttraumatic symptoms at baseline versus those with relatively lower levels of posttraumatic symptoms.

Motivation

Table 3 shows the means and standard deviations for the IMI outcomes. Since the intervention outcomes were moderated by gender, we provided motivation scores for the total sample and for the males and females separately. The analyses showed a significant difference between males and females with regard to interest/enjoyment (t (31) = 2.49, p = 0.018, η2 = 0.17), indicating that playing *Muse* was enjoyed more by males than by females. No difference was found for the total score and other subscales of the IMI.

Table 3. Intrinsic Motivation Inventory outcomes for the participants who played *Muse*.

	Total sample		Males		Females	
	Mean	SD	Mean	SD	Mean	SD
Total score	136.64	32.24	143.00	22.13	126.84	4.73
Interest/enjoyment*	23.27	8.87	26.15	7.52	18.85	9.24
Perceived competence	25.52	10.85	26.85	10.27	23.46	11.81
Pressure/tension	19.30	4.50	19.90	3.93	18.38	5.28
Perceived choice	37.15	6.88	39.35	3.91	33.77	9.04
Effort	23.21	6.54	23.70	6.18	22.46	7.24
Value/usefulness	31.45	12.04	33.20	10.73	28.77	13.83

Note: SD: standard deviation. *Significant gender difference ($p < 0.05$).

DISCUSSION

The present study evaluated *Muse* as a game-based meditation intervention for traumatized adolescents in residential care. The primary aim of this RCT was to test the immediate intervention effects on posttraumatic symptoms and stress. As predicted, the results indicated that the participants who played *Muse* reported reduced levels of posttraumatic symptoms and stress compared to the participants in the control group. The mentor-reports showed only a marginally significant decrease in posttraumatic symptoms. At two-months follow-up, the participants in the *Muse* condition reported marginally significant lower levels of posttraumatic symptoms compared to the controls. Taken together, these results show that *Muse*, in addition to TAU, is more effective than TAU alone for traumatized adolescents in residential care, although caution is warranted with conclusions regarding the long-term effects and mentor-reports.

Secondary outcomes included the immediate intervention effects on anxiety, depression, reactive aggression, proactive aggression, and executive functions. We found larger decreases in self-reported anxiety, depression, reactive aggression, and proactive aggression for the participants in the *Muse* condition compared to those in the control condition. The mentor-reported results on reactive aggression, proactive aggression, and executive functions showed no differences between the conditions. The inconsistencies between the self-reports and the mentor-reports might be caused by differences in the perception of the adolescents themselves and their group home mentors. Many studies in residential youth care have reported differences in adolescent self-reported outcomes and those reported by their mentors (Bastiaansen et al., 2004; Grills & Ollendick, 2003; Schuurmans et al., 2018; Schuurmans, Nijhof, et al., 2020). One suggested explanation is that group care workers are more critical in adolescent progress assessments, which keeps them from noticing changes (Knorth et al., 2008). Thus, the mentors may not have noticed the expected improvements among the participants in the *Muse* condition.

Other secondary outcomes included long-term intervention effects measured two months after the intervention had ended. After two months, the intervention effect was only maintained on self-reported posttraumatic symptoms. However, caution is warranted regrading this finding, since this effect only reached marginal significance (p = 0.052). Improvements in psychopathology symptoms did not disappear after the posttreatment (T2) measurement. Instead, the participants' symptoms remained stable or were even more improved. Also, our exclusion criteria included trauma therapy before or at T1, but due to ethical concerns, we did not withhold these traumatized adolescents from further treatment after the intervention had ended. Thus, between the T2 and FU measurements, some participants received trauma therapy. This may explain the decrease in posttraumatic symptoms in the control group at FU and have biased our outcomes. Yet, our main outcome from the self-reported posttraumatic symptoms still showed marginal significant differences between the conditions at the two-months FU measurement with a small-to-medium effect size. Previously, a pilot study exploring the feasibility of *Muse* in a sample of five participants showed that playing *Muse* not only resulted in immediate reduced posttraumatic symptoms, stress, and anxiety, but that these effects were maintained at one-month follow-up (Schuurmans, Nijhof, et al., 2020). Considering that effect sizes for long-term RCT outcomes on posttraumatic symptoms are usually small (Gutermann et al., 2017) and that our sample size was sufficient, but not very large, reaching marginal significance at two-months follow-up might indicate the long-term effect of *Muse* on posttraumatic symptoms.

The results from the exploratory analyses to evaluate the moderators indicated two potential moderators that need further discussion, namely gender and the baseline level of the posttraumatic symptoms. There are several possible explanations for the moderating effect of gender. First of all, it is established that videogame play is more popular among males than among females (Bonanno & Kommers, 2005). Motivation outcomes in this study showed that the males reported higher enjoyment with playing *Muse* than the females did, which could have led to a stronger intervention effect among the males, since motivation is a key predictor of treatment effectiveness (Harder et al., 2012). Another explanation for the moderating effect of gender may be found in sex-specific psychological, cognitive and biological mechanisms. Males, for example, tend to use a more active coping style to effectively deal with stress (Olff et al., 2007). This may not only lead to a lower risk of posttraumatic stress in males, but also contributes to their improvement in posttraumatic symptoms. A second moderating effect was participants' initial level of posttraumatic symptoms. We found a stronger intervention effect for the participants who reported higher levels of posttraumatic symptoms at baseline versus those with relatively lower levels.

This finding is hardly surprising, because there is the tendency of regression to the mean: average scores tend to go down in the groups with the highest initial scores and tend to go up in the groups with the lowest initial scores (Barnett et al., 2005).

The biggest strength of the current study is that, to our knowledge, this is the first full-scale RCT investigating the effect of a game-based intervention in a clinical context. This study was conducted among a high-risk sample of adolescents in residential (secure) care with clinical levels of posttraumatic symptoms. We did not exclude potential participants based on minimal IQ-score, comorbid disorders, such as autism, medication use, or concomitant forms of treatment (other than trauma-focused treatment), which is common practice and impedes the external generalizability of study results. Our study sample reflects the real-world population of adolescents in residential care and results require minimal translation to be implemented into clinical care.

Another particular strength is the use of a multi-informant approach with the participant's self-report as well as the mentor reports. Also, we included participants based on clinical levels of posttraumatic symptoms rather than a diagnosis of PTSD due to underdiagnosis (Miele & O'Brien, 2010). This need was illustrated by the characteristics of our sample: all participants were included based on clinically relevant posttraumatic symptoms, but only 28.57% (22 out of 77) were diagnosed with PTSD.

Importantly, we would like to discuss some of the limitations of this study. Both conditions received TAU, while the experimental condition received the *Muse* intervention as an additional treatment. Consequently, the participants who played *Muse* received extra individual attention compared to the control condition. An active control group would have controlled for this, but active control groups are only more rigorous when the participants in both conditions do not differ in their attention and expectations of improvement (Boot et al., 2013). Residential institutions have tight restrictions when it comes to casual gameplay, which made it impossible to implement a control group who played a game with no expected mental health benefits. We want to emphasize, however, that in the clinical setting, where this study was conducted, TAU included a wide range of evidence-based forms of treatment. The participants were only excluded if they already received treatment specifically targeting posttraumatic symptoms, so most of the participants received some form of concomitant treatment. This indicated that *Muse* effectively reduces a range of psychopathology symptoms, on top of the other treatments that were provided. Also, our aim was not to test the intervention's superiority over other forms of treatment, but to test whether the intervention was a beneficial addition to TAU, which makes TAU a valid control condition (Freedland et al., 2011).

Although the results of this study show the effectiveness of Muse, it remains open which aspect of the intervention ensured this effectiveness: the use of neurofeedback, the game-based format of the intervention, the relaxation tutorials, or other nonspecific effects. This is an avenue to pursue in future research.

To conclude, this randomized controlled trial shows that *Muse* is a promising intervention for traumatized adolescents in residential care. Immediately after the intervention, not only were posttraumatic symptoms and stress reduced, but anxiety, depression, and aggression were also decreased. Unfortunately, most of these improvements were not maintained at follow-up, leaving substantial room for intervention improvement and a need for future research. Thus, while additional studies are warranted, the present study provides strong support for the addition of game-based meditation approaches to traditional trauma-focused interventions.

Chapter 7

Effectiveness of game-based meditation therapy on neurobiological stress systems in adolescents with posttraumatic symptoms: a randomized controlled trial

Published as

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ABSTRACT

Many adolescents in residential care have experienced traumatic events and suffer from posttraumatic stress. Prolonged activation of neurobiological stress systems as the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis can result in long-lasting maladaptive alternations. This study investigated the effectiveness of *Muse*, a game-based meditation intervention, on sympathetic nervous system (SNS), parasympathetic nervous system (PNS), and cortisol basal activity and reactivity to acute stress among adolescents with posttraumatic symptoms in residential care.

The intervention consisted of two gameplay-sessions a week, for six consecutive weeks. Seventy-seven adolescents with clinical levels of posttraumatic symptoms (10 – 18 years old) received either *Muse* as an addition to treatment as usual (n = 40) or treatment as usual alone (n = 37). We expected reduced basal activity for the SNS and for cortisol, and increased basal activity for the PNS. As for the response to acute stress, we expected decreased PNS and increased HPA axis reactivity.

The Muse group exhibited lower basal activity for the SNS and increased HPA reactivity to acute stress. There were no differences between conditions on PNS and HPA axis activity during rest and on SNS and PNS reactivity to acute stress.

Game-based meditation therapy is a promising intervention for the treatment of adolescents with posttraumatic symptoms in residential care. Implications for clinical relevance and trauma-focused treatment purposes are discussed.

INTRODUCTION

Most adolescents in residential care have been exposed to multiple traumatic events such as domestic violence, neglect, or sexual, physical, or emotional abuse. Worldwide, rates range between 85% and 90% (Briggs et al., 2012; Collin-Vézina et al., 2011). Exposure to trauma increases the risk of psychological problems as anxiety, depression, aggression, and behavioral problems as sexual risk behavior and delinquency (Collin-Vézina et al., 2011; Smith et al., 2006). Traumatic experiences can also negatively affect youths' physical health (Afari et al., 2014) and their neurobiological stress systems (Bauer et al., 2002; Gunnar et al., 2006). These adverse effects of traumatic experiences are likely to continue over time without adequate treatment (Hiller et al., 2016). Therefore, the development of effective trauma interventions is critical.

Research on neural correlates of posttraumatic stress has shown dysregulation of neurobiological responses to stress (Bauer et al., 2002; Gunnar et al., 2006). In individuals without trauma history, stressors activate the autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal (HPA) axis systems. The ANS prepares the body for immediate action through activation of the sympathetic nervous system (SNS), prompting a rapid increase of cardiac output. When the stressor disappears, the parasympathetic nervous system (PNS) inhibits sympathetic activation and facilitates bodily recovery (Berntson et al., 2008). Whereas physiological changes due to SNS activation only take seconds, HPA activation follows a slower onset and longer duration. HPA axis activation results in the production of steroid hormones and is typically assessed by measuring its final product cortisol (Bauer et al., 2002).

Traumatic experiences such as domestic violence, neglect and emotional, physical, or sexual abuse result in repeated and prolonged activation of these stress systems, which can lead to autonomic and neuroendocrine dysregulation that last for long after the original stressor has disappeared (Bauer et al., 2002; Gunnar et al., 2006). Youths who suffer from posttraumatic stress can be highly physiologically reactive, even to mildly stressful stimuli. This over-reactivity is referred to as SNS-dominated hyperarousal and often leads to misinterpretation of other people's intentions and thus to persistent affective and interpersonal problems (Cook et al., 2005). The opposite of hyperarousal is PNS-dominated hypoarousal, which refers to under-reactivity and emotional numbing (Corrigan et al., 2011). Both hyper- and hypoarousal originate from dysregulation of sensory integration and self-regulatory capacities. A recent study among adolescents in residential care showed that adolescents with posttraumatic symptoms, compared to controls without posttraumatic symptoms, exhibited higher SNS, PNS, and HPA axis activity during rest. Additionally, for stress reactivity, adolescents with posttraumatic symptoms exhibited increased PNS reactivity and blunted HPA axis reactivity to acute stress (Schuurmans et al., 2021), which are characteristic for hypoarousal (Busso et al., 2017; Corrigan et al., 2011; Ouellet-Morin et al., 2019). Thus, traumatic experiences do not only increase the risk for a range of maladaptive psychological and behavioral outcomes, but can also lead to long-lasting alterations of neurobiological stress systems. Fortunately, at an early age, neurobiological systems contain a high level of plasticity (Bauer et al., 2002) and can be effectively altered by interventions (Slopen et al., 2014).

A novel approach that is assumed to address both physiological under- and over-regulation are meditation-based interventions, that are targeted at the baseline capacity to regulate one's emotions and physiological responses (Schuurmans et al., 2020; 2021; Spinazzola et al., 2011). A growing number of studies supports the shift from mainly cognitive oriented and verbally dependent therapies to interventions that target physiological sensations and stress regulation abilities (Gapen et al., 2016; Van Der Kolk et al., 2016; Warner et al., 2013). Specifically, interventions with a sensory-based approach that focus on bodily sensations and relaxation, such as meditation, have the potential for physiological impact. Indeed, among adolescents with posttraumatic symptoms in residential care, meditation-based therapy has been found to reduce posttraumatic stress (Schuurmans et al., 2021), increase attachment and self-regulation (Spinazzola et al., 2011b), and result in real-time improvements of SNS and PNS activity (Schuurmans et al., 2020). These studies show the potential for meditation-based interventions to improve neurobiological alterations after trauma. It is important to conduct research with adolescents, as dysregulation of the neurobiological stress system at a young age has been identified as one of the mechanisms through which traumatic events increase the risk of psychological, behavioral and physiological problems at a later age (Bauer et al., 2002; Gunnar et al., 2006; Miller et al., 2011).

Therefore, the current study conducted a randomized controlled trial (RCT) to evaluate whether a game-based meditation intervention (*Muse*) can improve neurobiological alterations among adolescents with posttraumatic symptoms. Game-based interventions are a novel strategy to engage adolescents into treatment by making use of their intrinsic motivation (Granic et al., 2014). Playing *Muse* as an intervention has been shown to reduce self-reported symptoms of posttraumatic symptoms, stress, anxiety, depression, and aggression (Schuurmans et al., 2021; Schuurmans et al., 2020). We expected that playing *Muse* as an addition to treatment as usual (TAU) would result in adaptive changes in neurobiological parameters towards the profile of controls without trauma history (Schuurmans et al., 2021). Specifically, for ANS parameters we hypothesized reduced SNS and increased PNS activity during rest and decreased PNS reactivity to acute stress, while for HPA axis parameters, we expected deceased basal activity and increased HPA axis reactivity for Muse participants.

METHODS

The current study used the neurobiological data that were collected as part of research project that included a RCT testing a game-based meditation intervention to decrease posttraumatic stress in adolescents with posttraumatic symptoms (Schuurmans et al., 2020, 2021). This research project was registered in the Netherlands Trial Register under ID NL6689; NTR6859 and ethical review and approval were provided by the medical-ethical committee Arnhem-Nijmegen under protocol NL58674.091.16.

Design, setting, and procedure

The current study was designed as a RCT evaluating the effectiveness of *Muse* as an addition to TAU on basal ANS and HPA axis parameters and ANS and HPA axis reactivity to social stress among a sample of adolescents with posttraumatic symptoms in residential care. Participants were recruited from three residential institutions in The Netherlands that provide open and secured residential care for adolescents with and without an intellectual disability (ID). When admitted to these institutions, adolescents filled in the Children's Revised Impact of Event Scale (CRIES-13) (Verlinden et al., 2014). For the current study, these data were used to screen for adolescents with a CRIES-13 score of ≥ 30 as eligible participants, since this score indicates clinical levels of posttraumatic symptoms. Due to the underdiagnosis of posttraumatic stress disorder in adolescents (Miele & O'Brien, 2010), we included participants based on clinically relevant posttraumatic symptoms rather than based on a PTSD diagnosis.

Inclusion criteria were: (1) CRIES-13 score ≥ 30; (2) age 10 to 18 years; (3) being able to comprehend and speak Dutch; (4) active informed participant assent; and (5) active parental or legal guardian consent for adolescents under the age of 16 years. Exclusion criteria were: (1) negative clinician advice, for example, when the participant already received other forms of treatment and the clinician feared that treatment burden would become too heavy (at this stage, participants were not randomized yet, so this exclusion criterium equally affected both conditions); (2) simultaneous participation in another clinical intervention study; (3) acute psychotic symptoms; and (4) a current or recent (within the last three months) trauma treatment, such as eye movement desensitization and reprocessing (EMDR) and trauma-focused cognitive-behavioral therapy (TF-CBT). There were no restrictions for concomitant interventions not targeting posttraumatic symptoms (e.g., medication, individual or group therapy). We kept track of the concomitant interventions and used these as covariates in the analyses. Participants received a €15 check at pre-test, a €10 check and a small present (stress ball) at post-test, and a €15 check at the two-month follow-up for hair cortisol (hC).

Sample

The present study used data from a RCT evaluating the effectiveness of playing *Muse* on posttraumatic symptoms. Adolescents with clinical levels of posttraumatic symptoms were assessed for eligibility (n = 135). Reasons for exclusion were current or recent trauma treatment (n = 19), adolescent or parent declined study participation (n = 11), adolescent would leave the institution soon (n = 13) or negative clinician advice (n = 10). A clinical sample of 77 adolescents with clinical levels of posttraumatic symptoms in residential care was recruited. The sample was 59.7% male (*n* = 46) with a mean age of 15.25 (SD = 1.79). Mean IQ score (retrieved from file analysis) was 86.42 (SD = 1.72). Adolescents were exposed to the following types of traumatic events: non-intentional traumatic events (e.g., an accident, severe illness, or a friend/family member who died; 100%), neglect (98.70%), domestic violence (98.60%), emotional abuse (90.90%), interpersonal traumatic events (85.10%), lost contact with parent for at least one year (66.20%), parent with psychiatric problems (44.10%), sexual abuse (27.30%), physical abuse (17.70%), death of a parent (8.60%). There were no baseline differences between the two conditions regarding age, gender, IQ score, disorder diagnoses, type of traumatic experiences or concomitant therapy. Detailed demographic and clinical characteristics per condition are described in Schuurmans and colleagues (2020).

Intervention

Muse. The *Muse* condition consisted of playing *Muse* in addition to TAU. *Muse* is a game-based meditation application with a brain-sensing headband that utilizes neurofeedback. In the current study, Muse was played on an iPad. The intervention consisted of two individual 15-20 minutes gameplay sessions a week for six consecutive weeks. Individual intervention schedules were dependent of participants' schedule for work, school and hobby activities, but the bi-weekly session days were scheduled with at least one day between (e.g., Monday and Wednesday or Tuesday and Thursday). *Muse* includes ten relaxation tutorials (e.g., deep-breathing techniques; Weisz & Kazdin, 2010), that are followed by three-minute meditation sessions. The gameplay sessions were supervised by research assistants who were trained to explain the tutorials according to the protocol. The participants completed at least two tutorials and two meditation sessions per intervention session. The brain-sensing headband provided real-time neurofeedback that was reflected by the intensity of the activity in the in-game environment that participants had selected previously (e.g., beach or rainforest). When the participant's mind was calm, the environment showed calm and settled winds, but these winds picked up and blew when the participant's mind became more active. After each meditation session, *Muse* provided participants with feedback on their performance in the form of points and awards that reflect participants' capacity to regulate their arousal. For a more detailed description of the *Muse* intervention, see Schuurmans and colleagues (2020).

Control condition. The control condition consisted of TAU: treatment as recommended by their clinicians, regardless of this study. Most common types of TAU were medication (*n* = 41), animal assisted therapy (*n* = 13), psychomotor therapy (*n* = 11).

Measures

Basal neurobiological parameters

Basal ANS activity: ANS measures were performed using electrocardiogram (ECG) and impedance cardiography (ICG) registration by the VU University Monitoring System (VU-AMS) (De Geus et al., 1995; Willemsen et al., 1996). Five electrodes were placed on the participants' chest and two on the back. Recordings were manually inspected and analyzed with the Data Analysis and Management Software (VU-DAMS) program version 4.0 (VU University, Amsterdam, the Netherlands). SNS activity was measured with pre-ejection period (PEP). PEP expressed in msec was derived from combined ICG and ECG recordings (Van Lien et al., 2013). PNS activity was measured with respiratory sinus arrhythmia (RSA). RSA can be influenced by respiration rate (RR) independently from PNS activity (Grossman & Taylor, 2007), so respiration rate (RR) (derived from the thorax impedance) was included as a covariate for RSA. To obtain basal ANS measures during rest, we conducted VU-AMS recordings during a 5-minute aquatic video (Piferi et al., 2000) that participants watched before the start of the stress task.

Basal HPA axis activity: hC levels pg/mg hair were derived to obtain a measure of basal HPA activity. Hair samples were cut as close to the scalp as possible from a posterior vertex position. Samples were taped on paper and stored in closed envelopes until sent collectively to the laboratory of endocrinology of the Erasmus Medical Center, Rotterdam, the Netherlands. Hair samples were washed in LC-MS grade isopropanol and after solid phase extraction, hair cortisol was quantified by liquid chromatography-tandem mass spectrometry (LCMS) (Noppe et al., 2015). At least 5 mg of the most proximal 2 cm of each hair sample was used for analysis – representing basal hC over the 8 weeks before the hair sample was taken. Thus, the pre-test hair sample was cut in week 8 and the post-test hC sample in week 16.

Neurobiological reactivity to acute stress during a social stress task

The stress task was an adapted version: the Trier Social Stress Task for Children (TRIER-C) (Buske-Kirschbaum et al., 1997) was combined with the Sing-a-Song Stress Test (SSST) (Brouwer & Hogervorst, 2014). We combined the speaking task with a song task rather than the traditional math assignment (Buske-Kirschbaum et al., 1997), to ensure comprehension. Participants received the introduction of a story and were told that they had five minutes to compose the end of the story before they would present their story for four minutes in front of a camera (Popma et al., 2006). Participants were recorded, allegedly for later assessment by a group of peers who would judge their performance. Then, participants were given a booklet with song texts and were told that they had to sing a song, also in front of the camera. Participants had thirty seconds to choose a song and had to sing the song aloud for thirty seconds. For detailed information on the measurement procedures, see the study protocol (Schuurmans et al., 2020).

Participants received specific instructions for the measurement session: light breakfast, no caffeine, no intense exercise or smoking immediately before the session and no alcohol or drugs use 24 hours before the measurement. To control for these potential confounding variables, participants were asked about their food/drinks, cigarette, alcohol and drugs use and sleeping/sporting behavior in general in the 24 hours before the measurement. Participants were assured that their answers would only be used for research purposes and would not be communicated to their group care workers or parents.

ANS reactivity: ANS parameters were measured with VU-AMS recordings during the following segments of the social stress task: [1] anticipation, [2] performing speech task, [3] anticipation song task, [4] performing song task, and [5] recovery.

HPA axis reactivity: sC samples (nmol/l) were collected before and after the stress task. Samples were collected between 13.00 p.m. and 17.00 p.m. using Cortisol Salivette collection tubes (Sarstedt, Nümbrecht, Germany). Six sC samples were collected: [1] twenty minutes before the stress task started (-20), [2] immediately before (pre), [3] immediately after (post), and [4] ten (+10), [5] twenty (+20), and [6] forty (+40) minutes after the stress task had ended. To establish a pre-task resting baseline, the first saliva sample (-20) was collected at least 20 minutes after participants entered the measurement room. Samples were stored at -20 degrees Celsius until sent collectively to the laboratory of endocrinology of the Erasmus Medical Center, Rotterdam, the Netherlands. Cortisol levels were measured using the LC-MS/MS method with the CHS MSMS Steriods Kit (Perkin Elmer, Turku, Finland) containing $^2H_3$-cortisol as internal standard. Chromatographic separation was performed on a Waters (Milford, MA, USA) Acquity UPLC HSS T3 1.8μm column and quantified by tandem mass spectrometry using a Xevo TQ-S system (Waters, Milford, MA).

Randomization, masking and sample size

The participants were randomly allocated (1:1 ratio) into two conditions. The Python script randomization was executed by the first author and stratified by gender and ID (ID versus no ID) to ensure equal ratios in both conditions. The allocation of the conditions was not masked. It was not feasible to blind participants or mentors, but they were not informed about the specific hypotheses and were only told that *Muse* was designed to help participants cope with general stress.

As the current study used data that were available from another RCT, an a priori power analysis was not available. Therefore, we conducted a post-hoc power analysis.

Statistical analyses

To compare both conditions on neurobiological basal activity during rest, multivariate analysis of variance (MANOVA) were used to compare post-test parameters between the two conditions with pre-test parameters as covariates. To evaluate intervention effects on neurobiological reactivity to acute stress, we followed Lindauer and colleagues (2006) and calculated three reactivity variables for each physiological parameter: (1) *baseline*, (2) *response*, and (3) *recovery*. The *baseline* score for ANS parameters was calculated as the mean basal score during rest, while watching the aquatic video. For sC, sample 2 (pre: taken immediately before the stress task started) was used for *baseline*, since stressors cause an increase in cortisol levels that peaks after approximately 15 minutes (Bauer et al., 2002). The *response* for ANS parameters was calculated as the mean score on recordings during the following phases of the stress task: anticipation speech task, speech task, anticipation song task, and song task. The *response* for sC was calculated as the mean score on sample 3 (post: taken immediately after the stress task ended) and sample 4 (+10: taken ten minutes after the stress task ended). The *recovery* for ANS parameters was calculated as the mean score during the recovery phase of the stress task. For sC, *recovery* was calculated as the mean score of sample 5 (+20: taken twenty minutes after the stress task ended) and 6 (+40: taken 40 minutes after the stress task has ended). MANOVAs were used to compare the post-test *baseline*, *response*, and *recovery* scores for the two conditions, using the pre-test measures as covariates.

In the RCT, evaluating the effectiveness of *Muse* on psychopathology outcomes (Schuurmans et al., 2021), it was found that participants who played *Muse* reported reduced posttraumatic symptoms. To explore whether potential improvements on neurobiological parameters are associated with improvements on posttraumatic symptoms (primary outcome), we conducted chi-square tests for significant neurobiological outcomes. Outcome change on posttraumatic symptoms (declined/no change/improved) was calculated with the Reliable Change Index (RCI) method (Tröster et al., 2007).

Covariates

Variables that were considered as potential covariates were smoking (number of cigarettes), alcohol (number of consumptions) and caffeine use (number of consumptions) in the 24 hours before testing, lifestyle smoking (average number of cigarettes a day), alcohol use (average number of consumptions a week), sporting behavior (average hours a week), eating behavior (average daily meals and snacks), medication use, comorbid psychological and physiological disorders. Additional covariates considered for salivary cortisol were hormonal contraception, menstrual cycle phase, hours of sleep the night before testing, season (as cortisol peaks in spring), time of testing (as cortisol concentrations decrease during the day), storage time and participants' age. For hair cortisol, additional covariates were hair treatment (i.e., dying/bleaching; yes/no) and hair washing (times a week).

RESULTS

Data inspection revealed missing data due to participant dropout at T2 (5.19%; $n = 4$) or to technological issues related to the physiological outcome measurements such as movement during recording, not enough saliva (sC) or hair (hC) in the sample, or laboratory processing problems (sC and hC). Outcome data were missing for HR (T1: 5.62%; T2:16.95%), PEP (T1:8.23%; T2: 18.55%), RSA (T1: 6.06%; T2: 17.16%) sC (T1: 9.52%; T2: 10.82%), and hC (T1: 19.48%; T2: 48.05%). Logistic regression analysis indicated that data were missing at random. Missing data were imputed using full information maximum likelihood estimation for Markov Chains. The PEP, RSA, sC and hC data were positively skewed and log^{10} transformed (Houtveen et al., 2002). For reasons of physiological meaningfulness, means and SDs for hC and basal PEP, and RSA in Table 1 show absolute values instead of transformed values. Analysis outcomes with imputed, transformed data are reported. All analyses were conducted with completers-only data too. These results showed minimal differences and led to the same statistical outcomes. At pre-test, there were no significant differences between the two conditions (see Table 1). Significant variables that were included as covariates were: age, gender, medication use, season, smoking (number of cigarettes), alcohol and caffeine use (number of consumptions) in the 24 hours before testing.

Main outcomes

Table 1 shows the means and standard deviations for all outcome variables per condition, and the statistics of all outcome analyses. At pre-test, there were no significant differences between the conditions (all $p < .10$). At post-test, participants in the *Muse* condition showed increased levels of basal PEP parameters ($p < .001$) and increased sC response to acute stress ($p = .017$). Post-hoc power analysis for MANOVA: repeated measures, within-between interaction with an effect size of $\eta 2p$ .08 showed that this study was powered with 70.96% power. To achieve 80% power to detect a difference between condition, the sample should have been 95 participants.

Table. 1 Neurobiological parameters at pre-test and post-test.

	Descriptives				Statistical outcomes		
	Muse (*n* = 37)		Controls (*n* = 40)				
	Mean	SD	Mean	SD	F *(df)*	*p*	η2p
Pre-test (T1)							
Basal ANS activity							
PEP baseline	92.02	18.36	88.17	19.61	.82 (1, 67)	.369	.01
RSA baseline	63.41	31.39	76.97	49.63	.89 (1, 67)	.350	.01
Basal HPA activity							
hC	3.20	1.72	4.10	2.26	2.33 (1, 71)	.131	.03
ANS reactivity							
PEP response	86.95	20.84	83.44	20.50	.10 (1, 67)	.750	.00
PEP recovery	86.16	20.23	82.21	20.59	.44 (1, 67)	.511	.01
RSA response	65.44	31.39	69.70	33.21	.78 (1, 67)	.381	.01
RSA recovery	69.96	33.59	78.64	44.78	.60 (1, 67)	.442	.01
HPA reactivity							
sC baseline	1.83	.87	1.83	1.25	.63 (1, 71)	.431	.01
sC response	1.60	1.03	1.60	.96	.74 (1, 71)	.394	.01
sC recovery	1.27	.52	1.29	.57	.09 (1, 71)	.763	.00
Post-test (T2)							
Basal ANS activity							
PEP baseline	105.02	12.57	84.66	19.53	31.00 (1, 61)	<. 001	.32
RSA baseline	69.12	37.06	75.32	39.97	.03 (1, 61)	.862	.00
Basal HPA activity							
hC	2.78	1.29	3.80	1.92	3.51 (1, 67)	.065	.05
ANS reactivity							
PEP response	104.37	11.85	87.18	18.02	1.32 (1, 61)	.255	.02
PEP recovery	104.86	11.68	86.72	18.52	.38 (1, 61)	.542	.01
RSA response	67.76	29.23	72.67	33.40	.71 (1, 61)	.401	.01
RSA recovery	69.65	29.84	70.91	33.40	.86 (1, 61)	.359	.01
HPA reactivity							
sC baseline	1.69	1.18	1.99	1.32	1.68 (1, 67)	.144	.03
sC response	1.66	.81	1.62	.78	5.96 (1, 67)	.017	.08
sC recovery	1.41	.72	1.42	.61	1.67 (1, 67)	.202	.02

Note. ANS: autonomic nervous system; PEP: pre-ejection period; RSA: respiratory sinus arrhythmia; HPA: hypothalamic-pituitary-adrenal; hC: hair cortisol; sC: salivary cortisol. hC is measured as pg/mg. sC is measured as nmol/l.

DISCUSSION

The present study is among the first to examine the impact of treatment on neurobiological parameters among adolescents with posttraumatic symptoms in residential care. The current study utilized a RCT to test whether game-based meditation therapy would restore neurobiological alterations after trauma. We hypothesized that participants who played *Muse* as an addition to TAU would show reduced SNS and increased PNS activity during rest and decreased PNS reactivity to stress. For the HPA axis, we expected decreased HPA axis activity during rest and increased HPA axis reactivity to acute stress. These hypotheses were partly supported. As predicted, the results indicated that participants in the *Muse* condition exhibited lower SNS activity during rest and increased HPA reactivity to acute stress. Contrary to our expectations, results showed no differences between conditions on PNS and HPA axis activity during rest.

The observed improvements on SNS and cortisol outcomes are consistent with research among adults, in that both trauma-focused treatment (Pascoe et al., 2017) and meditation (Boyd et al., 2018) can affect neurobiological parameters. We were unable to detect effects on basal PNS and basal HPA axis activity, but basal HPA activity was marginally significant. Therefore, the lack of a significant effect for HPA activity may likely been due to the lack of power in the current study. Future studies with adequate power are needed.

Among possible reasons for the lack of an effect on basal PNS activity are the small sample size of the current study and the complex nature of neurobiological parameters. It is theorized that PNS activity is a marker of emotional regulation, whereas SNS activity is a marker of behavioral activation and inhibition (Beauchaine, 2001). As there are indications that inhibition precedes emotional regulation (Campos et al., 2004), it might be that changes in SNS activity would take longer. Also, according to the neurovisceral integration model (Thayer & Lane, 2000) dysregulations in baseline sympathetic arousal are the result of parasympathetic disinhibition. Thus, the reduced levels of sympathetic activity that were found in this study, may be mediated by increased parasympathetic activity during meditation that did not generalize to situations further than the meditation sessions. However, this remains speculative and requires future research, since we did not measure SNS or PNS parameters during meditation in the current study.

Although a feasibility study showed that participants exhibited increased real-time PNS parameters while playing *Muse* (Schuurmans et al., 2020), which is in line with other studies reporting on increased parasympathetic activation during therapy sessions (Sack et al., 2008), we were not able to find an effect of playing *Muse* on SNS or PNS reactivity during the stress task. Other than the lack of power in the current study, this may be due to the short reaction time of ANS parameters to stress (Berntson et al., 2008). We might not have been able to detect changes in ANS reactivity because our sample size did not allow for more dynamic analyses other than time frames. HPA reactivity, on the other hand, has a slower onset and longer duration (Bauer et al., 2002), and therefore changes in HPA reactivity could be detected.

In the current study it was found that decreases in sympathetic activity (i.e., higher PEP) during rest were associated with decreases in self-reported posttraumatic symptoms, which is in line with research stating that low levels of sympathetic activity are associated with decreased feelings of fear (Raine, 2002) and threat (Blascovich, 2008). An interesting avenue to pursue for future research would be to examine the causality of this relation. Although decreases in physiological arousal are theorized to precede cognitive changes (Nishith et al., 2002), the relation between physiological and psychological parameters is complex. More research should be conducted on this topic.

Strengths and limitations

Our study has several strengths, which lie mainly in the broad coverage of neurobiological stress systems (i.e., the SNS, the PNS, and the HPA axis) as well as the utilization of a RCT design to test both resting activity and acute reactivity to social stress. In addition, this study was conducted in a high-risk sample of adolescents in residential care with clinical levels of posttraumatic symptoms. We did not exclude potential participants based on minimal IQ-scores, comorbid disorders, medication use, or concomitant forms of treatment (other than trauma-focused treatment), which is common practice and impedes the external generalizability of study results. Our study sample reflects the real-world population of adolescents in residential care and results require minimal translation to be implemented into clinical care.

In spite of the strengths, there are also several methodological limitations that should be considered. First and foremost, a post hoc power analysis showed that the study was underpowered. Therefore, we may have not been able to detect some effects that would have been significant if an adequately powered study would have been conducted. Also, except for the baseline measurement at start of the stress test, we performed no control test that compared the stress task measures to a non-stressful condition. The study utilized a repeated measure testing design that may have allowed for a practice effect. Participants might have had expectations at the second measurement. Some participants may have been extra anxious to the repeated testing, while others may have habituated to the measurement procedures. Yet, the used laboratory stress task has been shown highly effective to induce stress (Dickerson & Kemeny, 2004; Kudielka et al., 2004). Furthermore, although participants were assured that their answers about cigarette, drug and alcohol use were confidential and only for research purposes, socially desirable responses cannot be ruled out. As these potentially confounding variables were not biochemically verified, it might be that these have affected the outcomes of neurobiological variables.

Conclusions

In summary, our data show that playing *Muse* not only affects psychopathological outcomes as measured with questionnaires (Schuurmans et al., 2021), but that its effects can be observed in physiological parameters too. These physiological changes are not restricted to acute effects during therapy sessions alone (Schuurmans et al., 2020), but effects can also be observed in neurobiological resting activity and acute reactivity to stress after playing *Muse* has ended. To our knowledge, this is the first study to examine neurobiological changes after treatment in adolescents with posttraumatic symptoms. Our results indicate the potential of game-based meditation therapy to restore alterations of neurobiological stress systems.

Chapter 8

GENERAL DISCUSSION

The aim of the present dissertation was threefold. First, we aimed to provide insight into the dysregulation of traumatized youths' neurobiological stress systems by comparing a sample of traumatized youth to a non-traumatized control group. Second, we wanted to evaluate the accuracy and predictive value of a wearable wristband. Compared to traditional monitoring systems, this wristband provides a simpler and less invasive way to measure neurobiological stress parameters, thus increasing the feasibility of research. Furthermore, the wristband has the potential to become a valuable addition to physically focused treatment approaches. The third aim pertained to the evaluation of a game-based meditation intervention for traumatized youths in residential care. Through a feasibility study, we selected the intervention that was the best fit for our population, which appeared to be *Muse*. We tested the effectiveness of *Muse* to reduce posttraumatic symptoms and stress (psychopathological outcomes), and to normalize alterations in neurobiological stress systems (neurobiological outcomes). In the final chapter of this dissertation, the main findings are summarized and discussed in the light of existing knowledge. We reflect on the strengths and limitations of these studies and on the implications for future research and clinical practice.

MAIN FINDINGS

PART I: ALTERATIONS OF NEUROBIOLOGICAL STRESS SYSTEMS

The first part of this dissertation aimed to provide insight into the dysregulation of youths' neurobiological stress systems. Therefore, we made a comparison between traumatized adolescents and a non-traumatized control group in relation to their basal neurobiological activity and reactivity to acute social stress. Specifically, we investigated the hypothalamic-pituitary-adrenal (HPA) axis and the two branches of the autonomic nervous system (ANS): the parasympathetic nervous system (PNS) and the sympathetic nervous system (SNS). This study was described in **Chapter 2**, and showed that for the HPA axis traumatized adolescents, in comparison to a non-traumatized control group, showed increased long-term cortisol levels during rest, and blunted cortisol reactivity to acute stress. Outcomes in the ANS indicated that traumatized youths exhibited higher SNS (i.e., respiratory sinus arrhythmia [RSA]) and PNS (i.e., pre-ejection period [PEP]) activity during rest, and increased PNS (i.e., PEP) reactivity to acute stress. We found no difference between both samples in SNS (i.e., RSA) reactivity.

PART II: MEASURING NEUROBIOLOGICAL PARAMETERS

In the second part of this dissertation, we specifically focused on the measurement of neurobiological stress parameters**. Chapter 3** described a validation study that evaluated the accuracy and predictive value of the Empatica

E4, a wearable wristband to measure heart rate variability. While devices such as the VU-AMS are a valid way to monitor physiology, the application of sensors to the chest and back can be invasive for vulnerable, clinical populations. Simpler and less invasive monitoring systems such as wearable wristbands yield high expectations, but there is still debate about the validity of these wearables. The outcomes of this validation study indicated the potential of the Empatica E4 to measure HRV in an unobtrusive way. For several parameters, significant correlations were found between the Empatica E4 and the VU-AMS recordings. Although statistical analyses detected differences between the two devices for all parameters but heart rate, effect sizes were small. The predictive value for clinical care was also tested, and for all parameters except one, testing outcomes based on Empatica E4 recording led to the same conclusions as those that were based on VU-AMS recordings. These outcomes indicated the potential of the Empatica E4 as a practical and valid tool for research on heart rate variability in non-movement conditions when people are at rest.

PART III: GAME-BASED MEDITATION THERAPY

As described in **Chapters 4, 6, and 7**, the third part of research in this dissertation was comprised of clinical trial studies testing game-based neurofeedback meditation therapy for traumatized youths in residential care. Our first step was to conduct a feasibility study to assess the potential of three game-based meditation interventions that incorporated bio- or neurofeedback. **Chapter 4** described the results of this study, showing that *Muse* was evaluated as being the most positive of the three interventions. We found that participants showed improved physiological stress regulation during the meditation sessions of all three interventions. *Muse* was rated highest on user evaluations, and demonstrated the most robust overall improvement for psychopathological outcomes. All participants who played *Muse* showed reliable improvements (reliable change indexes [RCIs]) in posttraumatic symptoms, stress, and anxiety.

Based on the results of the feasibility study, an RCT was conducted to test the effectiveness of *Muse*. **Chapter 6** described the psychopathological outcomes, like posttraumatic symptoms and stress. We found that playing *Muse* as an addition to treatment as usual (TAU) resulted in greater improvements than TAU alone on self-reported posttraumatic symptoms, stress, anxiety, depression, and aggression. Mentor-reported posttraumatic symptoms showed marginally significant decreases for *Muse* participants compared to the control condition.

In **Chapter 7**, the effectiveness of *Muse* on neurobiological outcomes is described. Based on the outcomes of the comparison study described in **Chapter 2**, we expected increased basal activity for the PNS and reduced basal activity for the SNS and for cortisol. As for the response to acute stress, we expected decreased PNS and increased HPA axis reactivity. Traumatized youths who played *Muse* exhibited lower basal activity in relation to the SNS and increased HPA reactivity to acute stress. There were no differences between conditions in SNS and HPA axis activity during rest and in SNS and PNS reactivity to acute stress.

REFLECTIONS ON MAIN FINDINGS

PART I: ALTERATIONS OF NEUROBIOLOGICAL STRESS SYSTEMS

In part I of this dissertation, neurobiological stress systems were investigated in traumatized adolescents and non-traumatized controls. The advances of neurobiological measurement techniques have resulted in increasing attention devoted to the relation between neurobiology and psychopathological outcomes. Neurobiological parameters in traumatized adolescents are potentially important markers of stress sensitivity. They can indicate increased subsequent vulnerability to stressful events (McLaughlin et al., 2015; McLaughlin, Alves et al., 2014) and predict treatment effectiveness (Lipschutz et al., 2017; Van De Wiel et al., 2004). Yet, whereas nearly all studies on adolescents have focused on either the ANS or the HPA axis separately, the study described in **Chapter 2** evaluated both basal activity during rest and reactivity to social stress of the ANS, as well as the HPA axis. Outcomes showed differences between both samples. The neurobiological profile that was found in the group of clinically traumatized adolescents showed a blunted HPA axis response and a PNS-dominated ANS response, which are characteristic for under-reactivity to stressful stimuli, also termed hypoarousal (Busso et al., 2017; Corrigan et al., 2011; Ouellet-Morin et al., 2019).

The finding that traumatized youths in residential care exhibit hypoarousal – or under-reactivity – can increase the accuracy of trauma assessment and consequently improve treatment specificity and effectiveness. In **Chapter 1**, the general introduction, we outlined the fact that most youths are admitted to residential care for externalizing problems such as aggression (Connor et al., 2004) and that treatment approaches mainly target externalizing problems (De Swart et al., 2012). We should be aware that many of these traumatized youths may show under-reactivity to stressful stimuli, which is associated with symptoms such as flat affect, numbing, collapse, and dissociation (Corrigan et al., 2011). However, it is mostly youths' externalizing behavior that is the focus of attention for parents as well as professionals (De Reyes & Kazdin, 2005; Granic, 2014). **Chapter 1** also asserts that for many youths in residential care, their trauma goes unrecognized and untreated. To increase the accuracy of trauma assessment, we should be more attentive to posttraumatic symptoms like flat affect, emotional numbing, and dissociation. These are more difficult to recognize compared to observable externalizing behavior, but are associated with high levels of trauma exposure and posttraumatic symptoms (Brand et al., 2016; Castillo et al., 2014; Hagen et al., 2015) and can prolong or exacerbate long-term psychological problems (Folette et al., 2015).

Even though accurate trauma assessment is critical, currently practices still have room for improvement. All studies in the current dissertation included traumatized youth. Due to the underdiagnosis of posttraumatic stress disorder (PTSD) among youths (Miele & O'Brien, 2010), we included participants based on clinical levels of posttraumatic symptoms rather than a diagnosis of PTSD. The fact that all participants exhibited clinically relevant posttraumatic symptoms, but that only 28.57% (22 out of 77) was diagnosed with PTSD, illustrates the need for increased accuracy in trauma assessment.

The potential improvements in trauma assessment may simultaneously lead to increased specificity of current treatment approaches, and therefore to increased treatment effectiveness. The two most widely used forms of trauma treatment, trauma-focused cognitive behavioral therapy (TF-CBT) (Cohen et al., 2012) and eye movement desensitization and reprocessing (EMDR) (Shapiro, 1989), are based on exposure and cognitive processing. Although the empirical literature remains inconclusive, it is often thought that traumatized individuals who exhibit hypoarousal, and in particular those who dissociate, respond less well to many treatment approaches (Burton et al., 2018; Cloitre et al., 2012; Van De Wiel et al., 2004). It is assumed that individuals in a state of hypoarousal dissociate and respond less well to exposure as well as to cognitive therapy, as exposure requires emotional engagement with distressing traumatic memories, and cognitive elements work through adaptive reappraisal of the traumatic memory and its integration into the memory (Cloitre et al., 2012).

Research on trauma treatment that targets hypoarousal is scarce, but the few available studies suggest that hypoarousal includes extensive loss of both cognitive and bodily skills, and that effective treatment needs a bottom-up approach, focusing on regaining access to these skills. Thus, while most treatments are aimed at down-regulation, hypoarousal needs up-regulation of the bodily rhythm (Brantbjerg, 2018, 2020, 2021). Key elements for targeting hypoarousal are: (1) developing bodily and mental capacity to stay present and explore with curiosity by gentle muscle-activation, with a focus on mutual regulation, as the therapist actively participates during the sessions, and (2) psychoeducation to learn about emotional and physiological responses as normal survival-reactions. This hypoarousal treatment approach resembles elements of mindfulness and meditation, which trains the subject in the neutral observation of appearing phenomena, but on top of this, it adds the training of bodily coping strategies to increase the capacity for self-regulation and the widening of acting/reacting abilities (Brantbjerg, 2018, 2020, 2021). The game-based meditation intervention that was tested in **Chapter 6** and **Chapter 7** included both neutral observation of bodily sensations and the practice of self-regulation strategies, and therefore appeared to be particularly suitable as an intervention for this population.

PART II: MEASURING NEUROBIOLOGICAL PARAMETERS

Part II of this dissertation focused on measurement methods in neurobiological research. Specifically, **Chapter 3** presented a validation study of the Empatica E4, in which a wearable wristband was validated to measure ANS parameters. Measurement of neurobiological parameters has developed as a useful tool in the study of posttraumatic stress. An advantage of neurobiological markers over traditional measurement methods such as questionnaires is that they do not rely on self- or observant-reported information, and are thus less subject to reporting bias. Also, ANS parameters are relatively easy to obtain, for example by the wearable wristband that has been evaluated in this dissertation, increasing its applicability in clinical practice.

The study described in **Chapter 3** provided an evaluation of the validity of a wearable wristband. Wearables are non-intrusive, relatively comfortable, and easy to wear. These provide an excellent and practical opportunity to collect data during multiple measurement time points, for example for the monitoring of ANS parameters during therapy sessions. This can contribute to improved insight into the potential change of patients' physiological parameters within one session and over time between multiple sessions. Many interventions include some form of physical relaxation exercises like deep breathing techniques (Weisz & Kazdin, 2010). The addition of wearables to measure physiological reactivity provides a relatively easy way to measure the effectiveness of these relaxation exercises, and the clinical applicability of physiological measurements seems to increase with the fine-tuning of methods.

In the general population, new technologies on health and wellbeing are relatively easily adopted, while the adoption of these new technologies in healthcare have a much slower pace (Tana et al., 2017). The use of wearables in clinical populations remains to date mainly limited to academic research contexts rather than a real-world application in clinical care. At this point, there is accumulating evidence indicating the validity of the Empatica E4 (McCarthy et al., 2016; Ollander et al., 2017; Schuurmans, de Looff, et al., 2020; van Lier et al., 2020; Zheng & Poon, 2016) the Polar watch (Caminal et al., 2018; Giles et al., 2016), and the Fitbit watch (de Zambotti et al., 2016; Diaz et al., 2015; Kang et al., 2017), but many other technological devices do not have peer-reviewed research to support their accuracy and validity (Piwek et al., 2016). This may be partly due to the contrasting natures of the fields of technology and science. While technological developments evolve quickly, conventional scientific research tends to be a relatively slow process that easily takes years. By the time that a device has undergone rigorous testing, its original technology might be outdated. Yet, there are several reviews that indicate the potential of technology to improve health care practices (e.g., Scholten & Granic, 2019).

One potential solution could be a shift towards research frameworks that go beyond traditional RCTs, for example single-case (SC) research. SC studies examine effects over time and draw inferences by using the participant as his or her own control (Kazdin, 2019). RCTs, on the other hand, require large numbers of participants for sufficient statistical power and therefore take a long time to conduct (Lobo et al., 2017). Although SD studies are conducted with one participant, the generalizability of findings can be shown through replication (Kazdin, 2019). Compared to traditional RCT's, SC studies are more suitable to evaluate individual treatment elements (Kazdin, 2019), such as intervention delivery with and without the addition of a wearable wristband to monitor physiological parameters. Also, SC studies do more justice to participants' individuality. While RCT outcomes are presented in terms of group means that do not capture individual differences, the implicit assumption is that that these group means can be used to understand individual behavior. Yet, outcomes at group level do not generalize to individual level when the mean and variance of processes are not stable over time and psychological processes are naturally individually variable and time-varying (Fisher et al., 2018; Molenaar & Campbell, 2009). Therefore, group generalizations may obscure genuine individual differences and consequently over- or underestimate the accuracy of RCT outcomes.

While most research on wearables tends to focus on the validity and reliability of the data provided by them, issues regarding privacy and security have received less attention (Tana et al., 2017). This discussion is not unique to wearables and extends to all situations where data are collected by commercial devices. These data are often collected and stored by the manufacturing company. While these data are often anonymized, the level of anonymity is often not sufficient for use in clinical healthcare. It has been shown that 'anonymous' data traces can be used to reveal people's identity (Cilliers, 2020; Piwek et al., 2016). Moreover, many people do not understand the need to protect their health information, and they do not know about the types of data that are stored by companies (Cilliers, 2020). Therefore, it is crucial that technological devices meet the demands that are required by healthcare for the privacy and security of patients' data.

PART III: GAME-BASED MEDITATION THERAPY FOR TRAUMATIZED YOUTHS

In part III of this dissertation, the effects of game-based meditation therapy on psychopathological and neurobiological outcomes were evaluated. The studies in **Chapters 4, 6, and 7** provided an evaluation of *Muse* as a neurofeedback meditation intervention. The intervention consisted of twelve game-play sessions that lasted for approximately thirty minutes.

Although the schedule of the game-play sessions was discussed with participants so as to reach agreement on the specific days and times, the study in **Chapter 4** was designed as a structured, randomized feasibility study, and the studies in **Chapters 6 and 7** were designed as RCTs. Therefore, the interventions were delivered following a protocol to allow for comparison between the different interventions in the feasibility study and to increase replicability of the RCTs. While

RCTs are considered 'the gold standard' in intervention research, they come with design constraints that limit participants' ability to freely choose an intervention that suits their needs, preferences, and personalities (Scholten & Granic, 2019). Thus, these structured designs may have limited participants' feelings of autonomy. When youths are free to choose where and when they play *Muse*, they experience greater autonomy, which is related to increased self-esteem and intrinsic motivation in general (Deci & Ryan, 2000), and also more specifically with game enjoyment and future game play (Ryan et al., 2006). Motivation is one of the most important predictors of treatment effectiveness (Van Binsbergen, 2003). Therefore, if youths' sense of autonomy can be enhanced, for example by letting them choose themselves when and where they play *Muse*, the reported intervention effects might be even more pronounced.

Interestingly, a non-structured approach, with youths individually playing *Muse* when and where they choose, would not include the element of game-play supervision. While the game-play sessions were not supervised by trained therapists or psychologists, but by research assistants with a BSc or MSc degree in healthcare, the effect of game-play supervision is potentially an important intervention element, as it has been show that a trusting relationship can provide valuable emotional support (Lenkens et al., 2020; Schenk et al., 2018). Although the research assistants followed a protocol to explain the tutorials and meditation sessions, obviously there were moments of casual discussion, for instance when the youths were picked up and brought back to their group homes or school classes. Taking into consideration the fact that therapeutic alliance is among the most important predictors of treatment effectiveness (Karver et al., 2006; Shirk & Karver, 2003), the effectiveness of youths' playing *Muse* in a non-structured, unsupervised setting is a great avenue to pursue in future research.

STRENGTHS AND LIMITATIONS

The current dissertation contributes to the extant literature in important ways. The comparison study is the first to examine not only basal activity, but also reactivity to the stress of both the ANS and HPA axis in a sample of traumatized youth in residential care. The game-based meditation intervention *Muse* was selected based on the results of a feasibility study that assessed three interventions. The studies that evaluated the effectiveness of *Muse* utilized a randomized controlled trial (RCT) design that is considered the gold standard in evaluating healthcare interventions (Schulz et al., 2010).

A particular strength of the current dissertation is its multimethod approach. We included both psychopathological and physiological outcomes to test intervention effectiveness. Many studies rely on data that are collected solely through questionnaires. Although the administration of questionnaires is less invasive and requires fewer logistical and financial resources, participants might give socially desirable answers, which could bias outcome reports. The use of objective measures of neurobiological parameters increases the reliability of our results. The RCT described in **Chapter 6** that evaluated the effectiveness of *Muse* on psychopathological outcomes was the only study in the current dissertation that is solely based on questionnaire data. However, for that study we have used different sources of information and included outcomes based on adolescents' self-reports, as well as outcomes reported by their mentors.

Conducting research in clinical care, particularly in (secure) residential institutions, can be challenging, and comes with experimental and practical limitations. Many factors related to the youths (e.g., comorbid disorders), practitioners (e.g., limited time), and institutions (e.g., restrictive policies) were difficult to control and increased experimental noise (Weisz et al., 2015). However, intervention effects that were found under very structured and precisely controlled settings may not generalize to the real-life situations due to the discrepancy between research and clinical practice. The studies described, however, were conducted in a representative, real-world sample and the results thus required minimal translation to be relevant for clinical care.

Each study is only as good as the methods that have been used. Specific limitations of the individual studies are discussed in the previous chapters that describe each study separately and will not be repeated here. However, there are two general limitations that need to be mentioned. First, one of this dissertation's strengths is at the same time a weakness, namely the clinical real-world sample. The participants who were described in the studies are a valid representation of the real-world population of youths in residential care. This means that many participants suffered from numerous behavioral and psychiatric comorbidities, received several forms of concomitant therapy or medication, or were moved to other group homes or another institution. In heterogenic samples like this, the existence of certain subtypes is likely. RCT outcomes are presented in terms of group means that do not capture intervention effects for individual participants (Kazdin, 2019; Molenaar & Campbell, 2009). To illustrate this, in **Chapter 6**, we describe the fact that we found stronger intervention effects among males compared to females, indicating a moderating effect of gender. Unfortunately, our sample size was too small for adequately powered exploratory analyses. Again, SC design studies may provide an alternative that allows for monitoring intervention changes at the level of the individual (Kazdin, 2019). SD studies may be more suitable for research among populations where it is hard to reach large numbers of participants.

A second general limitation of the dissertation is the main inclusion criterion that was used to select our participants with clinical levels of posttraumatic symptoms. The clinical scores of posttraumatic symptoms were based on one questionnaire that youths completed in the standard questionnaire battery that is used in the residential institutions. The reliability of this method of inclusion can be discussed as we do not know about the specific circumstances under which youths filled in this questionnaire. In some group homes, youths fill in these questionnaires independently, while in other groups their care workers will sit with them. Youths might have under- or overreported their problems or given socially desirable answers. However, this was our only opportunity to screen every individual who was admitted to the residential institutions, and thus to increase the representativeness of the sample. Also, many posttraumatic symptoms are experienced internally, and self-reports are considered the most reliable measures for internalizing symptoms (Bastiaansen et al., 2004; Grills & Ollendick, 2003; Hourigan et al., 2011; Lagattuta et al., 2012).

SUGGESTIONS FOR FUTURE RESEARCH

Ultimately, research gives rise to more questions than it can possibly answer. With each study, new questions are raised, and unanswered questions will remain. We found that traumatized youths in residential care exhibit a hypoarousal profile of neurobiological stress reactivity, which tends to be associated with internalizing symptoms (Corrigan et al., 2011). Internalizing symptoms, such as dissociation as a long-term response to traumatic events, have only recently been recognized as posttraumatic symptoms (American Psychiatric Association, 2013). Some measurement instruments, such as the Children's Revised Impact of Event Scale (CRIES-13; Verlinden et al., 2014), a questionnaire that screens for posttraumatic symptoms, are based on the 'classic' symptom clusters to diagnose posttraumatic stress disorder (PTSD): hyperarousal, avoidance, and intrusion (American Psychiatric Association, 2000), and do not include items that capture symptoms that are typical of hypoarousal. Fortunately, there are other questionnaires, such as the Child Report of Posttraumatic Symptoms (CROPS; Greenwald & Rubin, 1999) and the Parent Report of Posttraumatic Symptoms (PROPS; Greenwald & Rubin, 1999), that are not based on diagnostic criteria but on a wider range of posttraumatic symptoms. These do include items that go with hypoarousal (e.g., 'I "space out" when people are talking to me'). Thus, while the CRIES-13 may accurately identify overreacting traumatized youths with a hyperarousal profile, the CROPS and PROPS may be preferred when youths with both hyper- and hypoarousal need to be identified. Therefore, future research is warranted on the validity of trauma questionnaires in relation to hypoarousal.

Further research is needed first to investigate its effectiveness when *Muse* is played without supervision or in other populations. *Muse*'s mechanisms of change could be investigated by a dismantling study to test the specific working elements of *Muse*. The *Muse* intervention, as we designed it, could be compared to conditions with versions that have one specific intervention element removed or changed. For example, the intervention could be tested with and without neurofeedback, with its original meditation tutorials and with other tutorials, or as a stand-alone intervention, and as part of CBT.

The studies in the current dissertation have tested *Muse* according to a standardized intervention protocol. The intervention schedule was fixed and identical for all participants. Future studies could investigate different variations of this schedule to provide insight into the optimal number, duration, and scheduling of the game-play sessions and examine how variations affect treatment effectiveness. Also, future research is warranted on the effects of *Muse* in contexts where youths decide for themselves when they want to play it, as its promising outcomes may not be limited to the context of interventions in residential care, but could potentially reach further, and it could be implemented in community prevention programs, for example.

CLINICAL IMPLICATIONS

As stated in the introduction chapter of this dissertation, many youths in residential care are traumatized and suffer from posttraumatic symptoms that are hard to treat. Based on the outcomes of the studies described in the current dissertation, several clinical implications and recommendations can be made, both for *Muse* in particular and for game-based interventions in general.

Muse is a game-based meditation application that can be played on iOS and Android devices. It was developed by a commercial manufacturer and is thus already available to the general public. Essentially, playing *Muse* only requires an iPad and neurofeedback headband. The neurofeedback headband can be ordered online, and the application can be downloaded for free. A disadvantage for implementation in the Netherlands is that *Muse* is only available in English. We translated all tutorials to Dutch for the studies in this dissertation. Participants could play *Muse* as intended, but when the tutorials were provided, the sound on the iPad was muted, and the research assistants would explain the tutorials in Dutch to the participants. Although it is possible to play *Muse* with translations for players who do not speak English, this requires either recorded translations or someone who is trained to translate the tutorials during the game-play session.

This dissertation focused on the population of traumatized adolescents in residential care. Our research outcomes show that *Muse* is an effective form of intervention to reduce posttraumatic stress and other forms of psychopathology in this population. Yet, many studies show that meditation can improve a great variety of outcomes in both community and clinical populations (e.g., Lang et al., 2012). Mindfulness-based meditation interventions are even considered a stand-alone intervention for anxiety and depression (e.g., Blanck et al., 2018). In the studies described in this dissertation, *Muse* was delivered as a stand-alone, standardized intervention, but in real-life clinical contexts, therapists may be able to implement *Muse* in other forms of therapy. The meditation tutorials in *Muse* resemble elements of cognitive-behavior therapy (CBT) such as deep-breathing techniques (Weisz & Kazdin, 2010), so one possibility is to use *Muse* as an addition to traditional CBT. The tutorials and meditation sessions can be integrated relatively easily into CBT interventions. Yet, the options for implementation could be extended even more if it were possible to offer either Dutch as a language option in *Muse* or to provide recorded translations of the tutorials. Depending on the population, *Muse* could be played outside of the context of therapy. In residential institutions, youths usually have one or more 'resting hours' scheduled during the day, which they spend in their bedroom. In theory, these youths could play *Muse* during these moments of rest. Although there are likely to be practical issues that need to be considered before implementation (e.g., residential institutions usually have tight restrictions regarding phone and computer use), these are not insurmountable problems. Also, when youths can play *Muse* outside a therapy context, this also offers an opportunity to implement *Muse* in non-clinical community samples (e.g., in school contexts).

We have shown that game-based meditation therapy has the potential to not only reduce posttraumatic stress and other forms of psychopathology, but also to restore alterations of the neurobiological stress system. The studies described in the current dissertation are not the first studies to find promising effects of game-based bio- or neurofeedback interventions in clinical care (Kahn et al., 2009, 2013; Schuurmans et al., 2015, 2018; Wijnhoven et al., 2015, 2021). Therefore, it is important to consider the most optimal and effective implementation of these interventions in residential institutions, as well as in other contexts. Over the last decades, many digital tools and game-based interventions have been developed for mental health care. Unfortunately, there are also tools and interventions that have undergone scientific testing in the form of RCTs, but that are not used in clinical care (E-health Jeugdnetwerk, 2021). Among the reasons for this gap between science and clinical practice may be a lack of clear guidelines or protocols for implementation (Wentzel et al., 2016), and healthcare professionals who are not accustomed to digital tools and interventions (Wykes & Brown, 2016). Evidently, scientific studies are not always able to get their outcomes translated into real-world care. This may need a change in the perspective of intervention research, for example towards the 'design thinking' approach that aims to build a practical product or service that serves a specific need. One of the core tenets of design thinking is the practice of prototyping and testing with users *during* the development phase (Scholten & Granic, 2019). Studies that aim to test tools and interventions may want to reach out to clinical care at an early stage. This would not only be to understand the needs and motivations of the participants, but also those of healthcare professionals who are the people who need to adopt these tools and interventions in their working environment. Including them in an early stage of research could improve generalizability and lower the barrier to implementation in real-world settings.

WHAT DOES NOT KILL YOU MAKES YOU ~~STRONGER~~ WEAKER

"From life's military school.—What doesn't kill me makes me stronger."
—Friedrich Nietzsche*

The saying 'what does not kill you makes you stronger' is commonly used in popular language as an affirmation of resilience. Under certain, specific conditions, the saying is correct. For example, our immune system does grow stronger after being exposed to germs (Simon et al., 2015). Regarding resilience, we indeed grow stronger after being exposed to challenging situations. We are not born with fully developed emotion-regulation capacities. Young children who get upset need a care giver to help them regulate their feelings. Children can only further develop their emotional self-regulation skills after they have experienced feelings of frustration, anger, or grief (Ellis & Del Giudice, 2019). Yet, exposure to adverse but common real-world events is not comparable to traumatic experiences, such as neglect, violence, or abuse.

In society, we may want to believe the idea that each experience, as bad as it is, can also lead to something positive. It might feel comfortable to think that trauma can also toughen you up for the real world. However, traumatized youths who fight their way through life, and end up as strong and resilient individuals are the exception, not the rule. Their fortunate outcome is not *because of*, but *despite* their traumatic past. The commonly used saying 'What does not kill you makes you stronger' is one of the great untruths that continues to resonate in our culture, and which contradicts scientific evidence.

Traumatized youth are not less, but *more* likely to experience traumatic events again (Arata, 2006; Collin-Vézina et al., 2011). The comparison study described in **Chapter 2** provides insight into the neurobiology underlying this vulnerability. Traumatized youths differ from non-traumatized ones in both neurobiological activity during rest and reactivity to acute stress. The precise mechanism whereby traumatic stress can lead to long-term neurobiological dysregulation remains unknown, but it is likely that chronic activation of the body's stress systems change the morphology and functioning of the prefrontal cortex, the hippocampus, and the hypothalamus, which are the brain regions involved in stress responsivity (Bremner & Vermetten, 2001).

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* *Twilight of the Idols or How to Philosophize with a Hammer*, Epigrams and Arrows, no. 8, page 6 (1844-1900). Ironically, Nietzsche's own mental and physical health have not been characterized as particularly strong or resilient, although he is among the most influential philosophers of all time.

TO CONCLUDE

Traumatic experiences do not prepare youths to deal with the challenges they will encounter in their lives. Love, care, and safety do. Therefore, we need to provide the vulnerable youths in residential care with the best care that we can offer. The findings in this dissertation contribute to the further improvement of residential care in general and improved care for traumatized youths in particular. We provided insights into traumatized youths' neurobiological stress systems, state-of-the-art measurement methods, and the potential for game-based meditation therapy as a new, innovative intervention for traumatized youth.

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Nederlandse samenvatting

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In Nederland verblijven meer dan 20.000 kinderen en jongeren in de residentiële jeugdhulp. Deze jeugdigen kunnen niet meer thuis wonen door ernstige psychologische en/of gedragsmatige problemen in combinatie met een complexe thuissituatie. De overgrote meerderheid van deze groep jeugdigen, zo'n 85% tot 90%, heeft al op jonge leeftijd meerdere traumatische gebeurtenissen meegemaakt, waaronder blootstelling aan huiselijk geweld, fysieke of emotionele verwaarlozing, en fysiek, emotioneel, en/of seksueel misbruik. Blootstelling aan chronische, traumatische stress leidt tot ontregeling van het neurobiologisch stress systeem, en daarmee tot een verhoogd risico op psychologische en gedragsmatige problemen (bijvoorbeeld angst, depressie en agressie), middelengebruik, criminaliteit, en om – opnieuw – het slachtoffer te worden van seksueel misbruik.

Deel I Trauma en neurobiologie

Stress activeert verschillende systemen in ons lichaam, waaronder het autonome zenuwstelsel (ANS), bestaande uit het sympathische en parasympathische zenuwstelsel, en de hypothalamus-hypofyse-bijnier-as (HPA-as). Het sympathische zenuwstelsel van het ANS zorgt bij stress voor directe activatie van het lichaam (de vecht-of-vluchtreactie), en het parasympathische zenuwstelsel brengt het lichaam weer in een toestand van rust en herstel wanneer de stress is verdwenen. Een adaptieve reactie op stress zorgt voor zowel activatie van het sympathische zenuwstelsel als de-activatie van het parasympathische zenuwstelsel, gevolgd door het omgekeerde wanneer de stressor verdwenen is. Activatie van het ANS kost slechts enkele seconden. De HPA-as daarentegen heeft een langere aanlooptijd en blijft langer geactiveerd. HPA-as activatie zet verschillende processen in gang en zorgt uiteindelijk voor de productie van het hormoon cortisol.

Langdurige traumatische stress zorgt voor chronische activatie van het sympathische zenuwstelsel en de HPA-as, waardoor het ANS en de HPA-as ontregeld kunnen raken. Deze ontregeling van stress systemen wordt ook wel gezien als een van de mechanismen die zorgen voor de ontwikkeling en het in stand houden van psychologische en gedragsmatige problemen na trauma. Getraumatiseerde jeugdigen kunnen overreageren op stress en direct erg emotioneel reageren bij blootstelling aan een stressor. Ook het tegenovergestelde komt voor, namelijk dat jeugdigen niet meer lijken te reageren op stress en vrijwel geen emoties meer tonen. Onderzoek naar deze verschillende reacties op stress na langdurig trauma helpt om behandeling van getraumatiseerde jeugdigen specifieker in te zetten en daarmee de effectiviteit van behandeling te verhogen.

In hoofdstuk 2 worden ANS (sympathische en parasympathische zenuwstelsel) en HPA-as (cortisol) parameters van getraumatiseerde jeugdigen vergeleken met die van een niet-getraumatiseerde controle groep. Basale ANS activiteit werd gemeten met een ECG tijdens rust, en basale HPA activiteit werd gemeten met haarcortisol. ANS reactiviteit bij stress werd gemeten met een ECG tijdens de Trier Social Stress Task for Children (TRIER-C), en HPA reactiviteit bij stress werd in kaart gebracht door de afname van speekselcortisol tijdens verschillende momenten van deze taak. Vergeleken met de controlegroep, laten getraumatiseerde jeugdigen significant verhoogde sympathische activiteit, en juist verminderde parasympathische activiteit tijdens rust zien. Tijdens de stress-taak laten zij een verhoogde sympathische reactiviteit zien. Op de HPA-as parameters zien we een verhoogde basale HPA activiteit bij getraumatiseerde jongeren, en in hun haar werden hogere concentraties cortisol gemeten dan bij de controlegroep. Tijdens de stress-taak vonden we juist een verminderde reactiviteit van de HPA-as, dus een minder sterke stijging van het cortisol bij stress. Geconcludeerd kan worden dat zowel de ANS als de HPA-as bij getraumatiseerde jongeren ontregeld is. Een sterk punt van deze studie is de inclusie van zowel het ANS als de HPA-as. Beperkingen zijn de verminderde power, het gebrek aan een placebo stress-taak, en de complexiteit van fysiologische metingen.

Deel II Onderzoeksmethoden in de neurobiologie

De verschillende hartritme variabiliteit (HRV) parameters van het ANS worden meestal verkregen uit een elektrocardiogram (ECG) zoals de VU-AMS. Dit wordt ook wel gezien als de 'gouden standaard', daar de validiteit van deze metingen is aangetoond. Het maken van een ECG houdt in dat er verschillende sensoren op het lichaam worden aangebracht. Voor getraumatiseerde jeugdigen kan dit zeer stressvol zijn. Inmiddels zijn er ook minder invasieve meetinstrumenten in de vorm van polsbanden op de markt gekomen, echter is de validiteit van deze polsbanden nog niet eenduidig aangetoond. Hoofdstuk 3 van dit proefschrift beschrijft een validatiestudie waarbij de Empatica E4 polsband wordt vergeleken met de VU-AMS op nauwkeurigheid en voorspellende waarde van gemeten HRV parameters.

In totaal werden 345 HRV opnames gebruikt welke verzameld werden als onderdeel van een pilot studie (hoofdstuk 4). Bij vijftien participanten werden herhaaldelijk HRV parameters (RR, HR, SDNN, RMSSD, LF, HF, LF/HF) gemeten door zowel de Empatica E4 als de VU-AMS. De opnames van beide meetinstrumenten werden met elkaar vergeleken. Daarnaast werd gekeken of klinische testen met beide meetinstrumenten tot dezelfde conclusies zouden leiden. Voor alle HR en HRV parameters werden significante intraclass correlaties (ICC) gevonden tussen Empatica E4 en VU-AMS opnames. Er was geen significant verschil tussen Empatica E4 en VU-AMS opnames voor HR. Er werden wel significante verschillen gevonden tussen Empatica E4 en VU-AMS opnames voor alle HRV parameters behalve hartritme, echter met kleine effect sizes voor SDNN, LF, en HF. Voor alle HRV parameters behalve RMSSD, leidden de klinische testen tot dezelfde uitkomsten. Dit maakt dat de Empatica E4 een praktisch en valide instrument lijkt voor het meten van HR en bepaalde HRV parameters. Beperkingen zijn het kleine aantal participanten, het niet kunnen valideren van EDA parameters, en het gebruik van verschillende software voor data analyse. Toekomstig onderzoek zou zich kunnen richten op het gebruik van de Empatica E4 tijdens activiteit en de validiteit voor het meten van real-time veranderingen.

Deel III Behandeling voor getraumatiseerde jongeren

De vergaande en langdurige negatieve gevolgen van chronisch trauma vragen om effectieve behandeling. Ondanks de wetenschap dat de meerderheid van de jeugdigen in residentiële jeugdhulp getraumatiseerd is, worden de trauma's bij deze jeugdigen vaak niet herkend, en dus ook niet behandeld. De oorzaak hiervan ligt voor een deel bij de focus van residentiële hulp op externaliserend gedrag. Behandeling richt zich op het verminderen van gedragsmatige symptomen, terwijl de onderliggende oorzaken hiervan – de trauma's – blijven liggen. Gelukkig is er de laatste jaren een ontwikkeling gaande waarbij steeds meer aandacht is voor traumabehandeling en traumasensitief handelen, zowel binnen als buiten de residentiële jeugdhulp.

Wat traumabehandeling ook lastig maakt is dat jeugdigen vaak helemaal niet gemotiveerd zijn voor behandeling, met name jongeren in de residentiële jeugdhulp. Vaak hebben zij al vele herplaatsingen en behandelingen achter de rug, wat de motivatie voor behandeling niet ten goede komt. Ook spelen kenmerken van traumabehandeling vaak een rol. De meest gebruikte vormen van traumabehandeling zijn trauma-gerichte cognitieve gedragstherapie (TG-CGT) en eye movement desensitization and reprocessing (EMDR). Beide vormen van behandeling zijn effectief, maar alleen wanneer jeugdigen in staat zijn tot emotie-regulatie. Precies dat is erg lastig voor chronisch getraumatiseerde jeugdigen die snel overspoeld raken door hun emoties. Voor optimale effectiviteit van traumabehandeling bij deze jongeren, zou de focus eerst moeten liggen op het reguleren van emotionele en fysieke responsen. Lichaamsgerichte behandeling richt zich op fysiologische sensaties en stress-regulatie. Eerder onderzoek liet al zien dat de inzet van meditatie en ademhalingstechnieken bij getraumatiseerde jeugdigen kan leiden tot verbeteringen in het stressniveau, de emotie-regulatie, en cardiovasculaire activiteit.

De in deze dissertatie onderzochte meditatie interventie is een vorm van game-based therapie. Dit is een innovatieve manier om jeugdigen te bereiken en in behandeling gebruik te maken van hun intrinsieke motivatie. Het spelen van games is namelijk enorm populair onder jeugdigen. Daarnaast biedt game-based therapie de mogelijkheid om direct te oefenen wat je geleerd hebt – niet *denken,* maar *doen*. Daarom beschrijven de hoofdstukken 4 (pilot studie), 5 (study protocol), 6 (RCT), en 7 (RCT) in deze dissertatie studies naar meditatie therapie voor getraumatiseerde jeugdigen in residentiële jeugdhulp.

In hoofdstuk 4 werden drie vormen van game-based meditatie therapie (*Muse*, *DayDream*, en *Wild Divine*) getest onder 15 participanten. Het doel was om te onderzoeken welke van deze therapievormen het meest passend was voor getraumatiseerde jongeren in residentiële jeugdhulp. Tijdens de therapiesessies werd fysiologische ontspanning bij de participanten gemeten door middel van respiratory sinus arrhythmia (RSA). Bij alle condities lieten participanten een hogere mate van ontspanning zien tijdens de meditaties dan tijdens de meting direct aan het begin van de therapiesessies. *Muse* werd als beste beoordeeld door de participanten, met een gemiddeld cijfer van 8.42 op een schaal van 1 tot 10. *Day Dream* werd beoordeeld met een 7.07 en *Wild Divine* met een 5.53. Participanten die *Muse* speelden lieten op vragenlijstuitkomsten de grootste vooruitgang zien, met klinisch relevante verbeteringen in posttraumatische symptomen, stress, en angst. De bevindingen van deze pilot studie zijn veelbelovend, maar moeten door het kleine aantal participanten met voorzichtigheid worden geïnterpreteerd. *Muse* werd geselecteerd voor vervolgonderzoek met een randomized controlled trial (RCT). Beperkingen van deze studie zijn het kleine aantal participanten en het gebruik van completers-only data, waardoor geen causaliteit kan worden aangetoond.

Hoofdstuk 5 beschrijft het studie protocol voor een RCT om de effectiviteit van de game-based meditatie interventie, *Muse,* te testen. Een groep van 77 participanten werd op basis van willekeur verdeeld in twee groepen: een groep die enkel standaardzorg, oftewel Treatment As Usual (TAU) kreeg, en een experimentele groep die zowel TAU als de *Muse* interventie kreeg. Participanten in de experimentele groep speelden *Muse* twee maal per week, zes weken lang. In hoofdstuk 6 worden de effecten van *Muse* op de psychopathologische uitkomsten beschreven. Participanten die *Muse* hadden gespeeld, rapporteerden direct na de interventie significante verminderingen ten opzichte van de controlegroep op posttraumatische symptomen, stress, angst, depressie, en agressie. Direct na de interventie rapporteerden mentoren een marginaal significante vermindering van posttraumatische symptomen. Twee maanden later rapporteerden participanten uit de *Muse* groep nog een marginaal significante vermindering van posttraumatische symptomen ten opzichte van de controlegroep. Uitkomsten van deze studie laten zien dat game-based meditatie therapie een veelbelovende vorm van behandeling is, die effectiever is dan wanneer jeugdigen alleen TAU ontvangen. Sterke punten van deze studie zijn de populatie, welke representatief is voor de klinische doelgroep en het gebruik van meerdere informanten. Een beperking is het gebruik van een TAU controlegroep. Ook is het niet meetbaar welk element van *Muse* er nu voor zorgt dat de interventie effectief is, neurofeedback, het game-based format, de ontspanningsoefeningen, of andere elementen. Toekomstig onderzoek zou zich hierop kunnen richten.

Hoofdstuk 7, tot slot, beschrijft de effecten van *Muse* op de neurobiologische uitkomsten. Participanten in de *Muse* groep lieten na de interventie een lagere basale sympathische activiteit en een verhoogde HPA-as reactiviteit bij stress zien dan voor de interventie. Deze studie laat zien dat *Muse* niet alleen effect heeft op psychopathologie uitkomsten, gemeten door middel van vragenlijsten, maar dat de effectiviteit ook kan worden geobserveerd in fysiologische parameters. Daarnaast blijken fysiologische veranderingen niet beperkt tot real-time veranderingen tijdens de meditatie sessies, maar kunnen deze ook worden waargenomen nadat de interventie is afgelopen. Sterke punten van deze studie zijn het includeren van zowel het ANS als de HPA-as, en het RCT-design om zowel neurobiologische parameters tijdens rust als tijdens situaties van stress te vergelijken. Beperkingen zijn de lage power, het gebrek aan een controle test voor de stress-taak, mogelijke verwachtingen van de participanten, en de mogelijkheid dat een betekenisvolle covariaat niet werd geïncludeerd.

De opzet van deze dissertatie was drieledig. Allereerst wilden we inzicht krijgen in de ontregeling van het neurbiologische stress-systeem van getraumatiseerde jongeren. Ten tweede wilden we de nauwkeurigheid en voorspellende waarde van de Empatica E4 polsband meten in vergelijking met ECG. Ten derde wilden we een game-based meditatie interventie evalueren als behandelvorm voor getraumatiseerde jongeren in residentiële jeugdhulp. Met een pilot studie selecteerden we de interventievorm die het meest geschikt was voor onze populatie, *Muse*. Daarna testten we de effectiviteit van *Muse* om posttraumatische symptomen en stress te verminderen, en om de ontregelde stress-systemen van getraumatiseerde jongeren te normaliseren.

In de discussie van deze dissertatie worden de klinische implicaties van de studies uitgebreid besproken. Samengevat kunnen de onderstaande punten als de belangrijkste conclusies worden beschouwd:

Het neurobiologische profiel van getraumatiseerde jongeren in de residentiele jeugdhulp liet een verminderde reactiviteit van de HPA-as, en een door het parasympathetische zenuwstelsel gedomineerde ANS reactie bij stress zien, welke kenmerkend zijn voor onderreactiviteit bij stress, ook wel hypoarousal genoemd. Hypoarousal gaat vaak samen met verminderde emotie, apathie, en dissociatie, en zou ervoor zorgen dat individuen minder goed reageren op behandeling. Onderzoek noemt twee punten om hypoarousal te behandelen, namelijk: (1) het ontwikkelen van de lichamelijke en mentale capaciteit om in het heden te blijven en subtiele spieractivatie, en (2) psychoeducatie over emotionele en fysiologische reacties als normale overlevingsmechanismen. Met name het eerste punt bevat elementen van mindfulness en meditatie, wat game-based meditatie therapie een veelbelovende vorm van behandeling maakt voor deze groep jeugdigen.

De Empatica E4 lijkt een praktisch en valide instrument voor het meten van hartritme en HRV parameters. Dit biedt bijvoorbeeld de mogelijkheid om individuen tijdens ontspannings- of meditatie interventies een polshorloge te laten dragen, waardoor op een relatief gemakkelijke wijze de effectiviteit van deze interventies in kaart gebracht kan worden. Een sterk punt van deze studie is de uitvoering binnen de klinische praktijk, waardoor de resultaten daar met minimale vertaling kunnen worden toegepast.

Muse is een veelbelovende vorm van interventie voor jongeren met posttraumatische symptomen in residentiële jeugdhulp. Om wetenschappelijk onderzoek naar de effectiviteit van *Muse* uit te voeren, was het nodig om de interventie volgens een gestandaardiseerde en geprotocolleerde wijze uit te voeren. Hierdoor waren participanten niet vrij om *Muse* te spelen wanneer zij wilden, maar moest dit plaatsvinden volgens het protocol. Wanneer participanten meer vrijheid krijgen om zelf te bepalen wanneer zij willen spelen, zorgt dit voor een gevoel van autonomie, wat weer zorgt voor meer zelfvertrouwen en intrinsieke motivatie. Echter moet hierbij ook rekening worden gehouden dat het element van de therapeutische relatie dan wegvalt.

Curriculum Vitae

Curriculum Vitae

Angela Schuurmans was born on July 1st 1987 in Oss, the Netherlands. She has obtained degrees in Psychology and Health at Tilburg University (Bachelor's degree, with distinction), Behavioral Science (Research Master's degree, with distinction) and Philosophy (Master's degree) at the Radboud University Nijmegen, and Play Therapy (Master's degree, cum laude) at the Christian University of Applied Sciences. After her Bachelor's degree, Angela moved to Belgium. At the Catholic University of Leuven, she followed a one-year program on Neuropsychology and Genetics. After obtaining her Research Master's degree, Angela went abroad to England. She spent a semester at the University of Cambridge to study Psychology, Policy and Public Health and to contribute to a research project on public health care. Back in the Netherlands, she started her PhD research at the Behavioural Science Institute, Radboud University to study neurobiological stress-systems and to test a game-based meditation intervention to improve posttraumatic stress and neurobiological dysregulation among traumatized adolescents in residential care. Angela combined her PhD research with clinical education and work. As the desire to keep developing herself remained, Angela has started with a post-graduate clinical degree in family therapy (NVRG Systeemtherapeut). Angela is the founder of Praktijk Calm Kids, an outpatient mental health center for child and youth psychology and play therapy. Currently, Calm Kids has grown to a center with locations in Duiven and Zevenaar. Not only is Angela driven to provide individual children, adolescents and their parents with the best care possible, she also values contributing to mental health care innovation and development at a larger scale. Therefore, she works closely with other health care professionals and takes part in a collaborative initiative between public health teams and several regional mental health centers, to contribute from her expertise as a clinician and a behavioral scientist.

List of publications

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Dankwoord

Dankwoord

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