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The literature examining respiratory sinus arrhythmia (RSA) in individuals with post-traumatic stress disorder (PTSD) has increased over the past two decades. Research suggests that people with PTSD have lower RSA than individuals without PTSD. But these findings have been mixed. When assessed dimensionally within individuals diagnosed with PTSD, research also suggests that RSA is negatively correlated with PTSD symptom severity, but some failures to replicate have been reported and the overall magnitude of this effect is unknown, suggesting the need for a comprehensive meta-analysis. This meta-analysis of 50 studies (including unpublished data) examined the association between PTSD and RSA, and potential moderators of this association. A significant small effect size ($g$ = -0.22) was observed, with moderate heterogeneity. None of the moderator variables examined (i.e., control group, trauma type, PTSD measure, RSA measure, age, gender) explained the effect size's heterogeneity. Publication bias analyses suggested little evidence for publication bias among the meta-analysis findings. Overall, this meta-analysis provides clarity to the mixed literature surrounding the association between RSA and PTSD. However, future research should examine other potential moderating variables of this association.

# RESPIRATORY SINUS ARRHYTHMIA AND PTSD: A META-ANALYSIS

by

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TABLE OF CONTENTS

LIST OF TABLES

Page

LIST OF FIGURES

Page

# CHAPTER I

# INTRODUCTION

Posttraumatic stress disorder (PTSD) is a major public health issue and its prevalence continues to grow. It is estimated that 60 percent of males and 50 percent of females in the United States will experience a traumatic event in their lifetime. Of those individuals, 3.5% will go on to develop PTSD (Kessler et al., 2005). Research suggests a number of demographic and trauma-related factors are associated with PTSD including gender, race, age at which trauma occurred, social support, and past psychiatric history, to name a few (Brewin et al., 2000). However, in recent years, there has been a push to examine psychophysiological factors that are associated with PTSD. Research suggests that psychophysiological factors can be used as objective measures to determine the physical effects associated with PTSD (Bauer et al., 2013). Psychophysiological markers can expand upon what research has addressed in clinical interviews and self-report measures to better understand physiological symptoms in individuals with PTSD.

Understanding these physiological abnormalities is also crucial to better understanding the comorbidity between PTSD and physical health problems, and ultimately treating both problems. Individuals with PTSD are at greater risk for developing hypertension and coronary heart disease (Player & Peterson, 2011), both of which are public health issues. Much of the literature focuses on military samples finding

that veterans who report PTSD symptoms are also more likely to have a nonfatal myocardial infarction or onset of coronary heart disease (Kubzansky et al., 2007). Research has discovered similar findings in civilian samples, in that civilians with PTSD were at an increased risk for hypertension and vascular disorders (Dirkzwager et al., 2007; Kibler et al., 2009). With these findings there is a need to further examine cardiovascular functioning in PTSD samples.

Respiratory sinus arrhythmia (RSA) is one psychophysiological measure that provides a way to examine cardiovascular functioning. RSA is the beat-to-beat variability in heart rate, and a relatively pure measure of parasympathetic nervous system (PSNS) activity, not confounded with sympathetic arousal. RSA has gained substantial attention over recent years, and shows promise as a measure of physiological symptoms of PTSD (Zoladz & Diamond, 2013). Although the number of trauma studies including RSA has grown, the findings have been mixed, with some findings indicating that individuals with PTSD have lower RSA, but others finding no significant association between PTSD and RSA. These varied findings, along with the increase in the number of studies examining RSA in PTSD populations, suggest a present need to conduct a comprehensive meta-analysis to examine the overall size of the association between PTSD and RSA, to determine if PTSD is significantly related to RSA, and to examine potential moderators of the association between RSA and PTSD.

**Physiology of Posttraumatic Stress Disorder**

The distinct physiological symptom presentation of PTSD suggests evidence to support an association between the disorder and lowered RSA. Although the DSM

criteria for PTSD have evolved over the years, physiological symptoms have been an essential feature of symptom presentation since PTSD was first added to the DSM in its third edition (3rd ed.; DSM–III; American Psychological Association, 1980). DSM-5 includes the following psychophysiological symptoms (American Psychological Association, 2013):

- Marked physiological reactions to internal or external cues to symbolize or resemble an aspect of the traumatic event(s).
- Exaggerated startle response.

Indicators of sympathetic nervous system (SNS) responses have traditionally been examined in PTSD research through the use of startle or trauma cue exposure paradigms (Butler et al., 1990; Shalev et al., 2000). However, another component of the autonomic nervous system, the PSNS, has not received as much attention in the field. The PSNS is of particular interest because of its influence on resting heart rate. Resting heart rate is a decisive indicator of cardiovascular health, with an elevated resting heart rate putting an individual at greater risk for cardiovascular problems later in life (Fox et al., 2007). Research suggests that PSNS influences resting heart rate independently of the SNS (Bernston et al, 1991). Indeed, the PSNS has been found to influence heart rate more than the SNS (Katona et al., 1982), affecting cardiac control with a ratio of 7:1 in humans (Bernston et al., 1993), increasing the value of examining PSNS functioning.

In 2007, Pole conducted a meta-analysis on the psychophysiology of PTSD. The meta-analysis synthesized the literature examining markers of the autonomic nervous system, and found that individuals with PTSD display heighted SNS arousal through

stronger responses to startling sounds and trauma cues. This finding illustrates an increased reactivity driven by increases in SNS activity in response to trauma-related or threatening stimuli. The meta-analysis also found that PTSD was associated with higher resting HR and higher resting skin conductance (SC), which are both ways to measure baseline physiology of the autonomic nervous system. The association between PTSD and resting HR was larger than the association between PTSD and resting SC. Because resting SC is a means of assessing the SNS, whereas resting HR is affected by both the SNS and PSNS, Pole's finding suggests that resting arousal in PTSD is influenced by both the SNS and PSNS, instead of solely the SNS (Pole, 2007). While there is still value in understanding the role of the SNS in relation to PTSD, there is strong evidence supporting the need to use PSNS measures alongside SNS measures in clinical psychology (Bernston et al., 1991; Bernston et al., 1993; Katona et al., 1982). The PSNS is specifically in charge of relaxing or slowing body processes, and is often referred to as the "rest and digest" system (Malpas, 2010). By examining both systems, researchers will be able to see the full picture of how the autonomic nervous system is associated with PTSD and how it may impact an individual's health long term.

Respiratory sinus arrhythmia (RSA) is one way to quantify PSNS functioning. RSA is commonly used because it is seen as the purest way to measure PSNS functioning. RSA is the variability in heart rate relative to breathing rate. As one inhales, heart rate increases, and as one exhales heart rate decreases. RSA is used to measure cardiac vagal control (i.e., beat to beat variability in heart rate), or more simply how well your body regulates itself when at rest (Bernston et al, 1993), with high RSA indicating a

healthy PSNS. Porges (1995) suggests RSA can also be viewed as a measure of stress reactivity, and low resting RSA may serve as a risk factor for stress vulnerability. In general, high RSA means the body has good cardiac vagal control and is the PSNS is functioning well, while low RSA indicates poor cardiac vagal control and PSNS functioning.

RSA has become increasingly popular in psychological research because RSA can be measured noninvasively. RSA is collected via electrocardiographic (ECG) sensors placed on the torso, and at times, with an additional respiratory band. There are different ways to quantify RSA, which can be divided into two main categories of time-domain and frequency-domain. Time domain measures include the standard deviation of beat-to-beat intervals (SDNN), the root mean square of successive differences (RMSSD), and the fraction of beat-to-beat intervals that differ by more than 50 milliseconds (pNN50). Frequency domain measures include RSA and high frequency heart rate variability (HF-HRV). Time domain measures are based on the time-series of RR intervals, or the time between R peaks on an ECG reading. Frequency domain measures divides the heart rate signal into frequency bands and quantifies these bands into low or high frequency. High frequency is driven by the PSNS, whereas low frequency is influenced by both the SNS and PSNS. A single gold-standard measure within time or frequency domains has not yet been created, leading to controversies in the field as to which measure is most accurate and best captures PSNS functioning. Indeed, several different measures have been used to measure the association between PSNS functioning and PTSD in the literature.

**Respiratory Sinus Arrhythmia and Posttraumatic Stress Disorder**

The current literature suggests PTSD may be associated with lower resting RSA, although findings are mixed. Two types of study designs (between-groups and correlational) have been commonly used to examine the association between RSA and PTSD. The between-groups design is an examination of RSA in participants with PTSD compared to control groups. Studies suggest that individuals with PTSD have a lower RSA than healthy individuals or trauma exposed individuals without PTSD (Blechert et al., 2007; Chang et al., 2013; Cohen et al., 1997), although some studies have not found significant differences between groups (Bertram et al., 2014; Kirsch et al., 2015). The correlational design measures PTSD severity continuously and correlates symptom severity with RSA. Some research suggests PTSD symptom severity is negatively correlated with RSA (Song et al., 2011), whereas other studies have not found this result (Keary et al., 2009; Sahar et al., 2001).

Although findings are mixed, there is evidence that low RSA may be a physiological symptom of PTSD, rather than a risk factor for PTSD. Shah et al. (2013) examined HRV in 459 male veteran twins who were discordant for combat PTSD. The study found that only the twins with PTSD had lower HRV, and the inverse relationship between combat exposure and HRV was reduced when controlling for PTSD. These findings suggest low RSA may be a result of PTSD, and not a risk factor or biological predisposition to trauma exposure. Treatment outcome studies have also found an increase in RSA following treatment. Studies looking at treatment response in military populations found that treatment including mindfulness, relaxation training, and

biofeedback led to increased RSA (Bhatnager et al., 2013; Lewis et al., 2015; Reyes, 2015). Other studies found similar results with RSA increasing following treatments including cognitive-behavioral therapy, prolonged exposure, stress inoculation training, psychodynamic therapy, eye movement desensitization, and biofeedback in civilian populations (D'Andrea & Pole, 2012; Farina et al., 2015; Nishith et al., 2003; Sack et al., 2007; Zucker et al., 2009). Finally, RSA increased with psychotropic medication treatment in PTSD samples (Cohen et al., 2000).

Due to the mixed findings, there is a present need to synthesize the literature. To date, there has been one published meta-analysis examining heart rate variability (HRV), a way of measuring RSA, as a psychophysiological indicator of PTSD (Nagpal et al., 2013). Nagpal and colleagues (2013) examined the high frequency component of HRV along with several other RSA measures (e.g., RMSSD). The meta-analysis found HF-HRV and RMSSD to be significantly associated with PTSD, with effect sizes of $g = -2.27$ and $g = -2.94$, respectively. However, the meta-analysis only included studies with control groups, excluding all bivariate correlational data between HRV and PTSD symptom severity. They also did not include unpublished data in their results, which may subject their findings to an overestimate of the effect size due to publication bias, and did not examine potential moderators of the association between RSA and PTSD. The proposed study will expand upon these gaps in the previous meta-analysis to offer a more comprehensive meta-analysis that includes unpublished data, includes correlational data, and examines potential moderators of this relationship.

As with most biological constructs, there are many external factors that affect RSA. For this reason, it is crucial to examine potential variables that may moderate the association between RSA and PTSD. One important moderator to consider is age. Research suggests that RSA has higher variability at a younger age compared to older adults (Hirsch & Bishop, 1981), and RSA is subject to decreases over time (Masi et al., 2007). This research suggests that, when comparing youth with and without PTSD to adults with and without PTSD, there will be a greater association between PTSD and RSA in youth because of the increased level and variability in RSA at a younger age. However, age may also be connected to how long an individual has maintained symptoms of PTSD, leading to a decrease in RSA over time. Due to this connection with age, it is possible that older samples may display a larger association between RSA and PTSD. Despite the ambiguity of how age impacts RSA, I predict there will a larger association between RSA and younger samples due to the higher variability in RSA.

Another potential moderator of the association between PTSD and RSA is the type of control group used in independent-sample studies. Research suggests that individuals with other anxiety disorders have lower RSA than healthy controls. Pittig et al. (2013) found that people with panic, generalized anxiety, social anxiety, and obsessive-compulsive disorder all displayed lower HRV compared to healthy controls. The literature suggests that anxiety disorders express a common trait of reduced autonomic flexibility, leading too lower HRV (Friedman & Thayer, 1998). Similarly, a meta-analysis done by Kemp et al. (2010) found that depressed people also display lower HRV, and HRV is negatively correlated with depression severity. Due to these findings, I

predict that there will be a larger difference in RSA between participants with PTSD participants and healthy controls than between participants with PTSD compared with other mental health disorders. Consideration of trauma-exposed control groups is also necessary because these individuals experienced a traumatic event but did not develop PTSD, indicating resilience. When examining RSA in PTSD compared to trauma-exposed controls, some studies found no difference between groups (Martinez & Eliez, 2008; Sahar et al., 2001), suggesting that a trauma might reduce RSA even without the development of PTSD. Similarly, it is predicted that there will be a larger difference in RSA between individuals with PTSD and healthy controls than between individuals with PTSD and trauma-exposed controls.

Other moderators to consider include trauma type, which some research has suggested may be strongly connected to PTSD. Specifically, people who experience interpersonal traumas (e.g. sexual assault, abuse) have a greater probability of developing PTSD (Schumm et al., 2006) than non-interpersonal traumas (e.g. motor vehicle accident, natural disaster). Gender may be another moderator, as female gender is a risk factor for developing PTSD (Brewin et al., 2000). The final moderators to consider will be type of PTSD measure and type of RSA measure to examine any difference in the magnitude of the effect size based on the measure used.

Due to the mixed findings in the literature and potential variability in the association due to moderating variables, a comprehensive meta-analysis is needed to determine the overall size of the association between PTSD and RSA and to examine potential moderators of this overall effect. A meta-analysis takes a systematic approach

to first calculate effect sizes across relevant studies, and then combine these effect sizes to examine the robustness of the association between PTSD and RSA. The results of a meta-analysis can determine whether future studies are needed to further clarify an association. A meta-analysis can also draw out new hypotheses to be tested, particularly through the identification of moderators.

**Goals and Hypotheses**

The first goal of this meta-analysis is to combine existing findings to estimate the overall size of the association between PTSD and RSA and to determine whether PTSD is significantly related to RSA. The second goal of this study is to examine moderators of the relationship between PTSD and RSA (e.g., age, control group). Specifically, we predict that age will serve a significant moderator of the association between PTSD and RSA. It is expected due to high variability in RSA level in youth populations, there will be a larger effect in these populations compared to older adult populations. We also predict that the type of control group will serve as a significant moderator of the association between PTSD and RSA. It is expected that when PTSD groups are compared to healthy control groups, there will be a larger effect size than when PTSD group are compared to other control groups (i.e., trauma-exposed controls, other mental health disorders).

The study will also engage in exploratory moderator analyses to see whether there is an effect on the association between PTSD and RSA based on gender, trauma type, what measure is used to assess PTSD severity (i.e., clinical interview, self-report), along with what measure is used to quantify RSA (e.g., time-domain, frequency domain,

combined). Examining the overall effect size and moderators of this effect will help scientists and clinicians better grasp the association of PTSD and PSNS activity and clarify how strong this effect is. The final goal is to evaluate the extent of publication bias in the literature, in order to determine how accurate the observed effect size is.

# CHAPTER II

# METHOD

## Participants

The methods used in conducting this meta-analysis were in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, 2015). This method was developed in order to ensure best practices in conducting meta-analyses of clinical trials, but can also be utilized for other types of meta-analyses. The meta-analysis followed the subsequent steps as proposed by Cooper (2010): "1) formulating the problem, 2) searching the literature, 3) gathering information from studies, 4) evaluating the quality of studies, 5) analyzing and integrating the outcomes of studies, 6) interpreting the evidence, and 7) presenting the results."

## Study Retrieval

Several methods were used to ensure an exhaustive literature search. First, a computer search was conducted on July 5, 2016 across the following databases: PsycINFO (Psychological Information Database), PubMed, and PILOTS (Published International Literature on Traumatic Stress) databases. The following search terms were used: "PTSD," "post traumatic stress disorder," "post-traumatic stress disorder," or "trauma," combined with "RSA," "respiratory sinus arrhythmia," "HRV," "heart rate variability," "vagal control," or "parasympathetic nervous system.

**Study Inclusion and Exclusion Criteria**

At the full-text review stage, studies were assessed by Allison Campbell for eligibility based on the following inclusion and exclusion criteria:

Inclusion Criteria:

1. Study included a measure of PTSD
2. Study included a baseline measure of RSA
3. Study involved human participants

Exclusion Criteria:

1. Non-English article
2. No data presented (e.g., literature review)
3. Duplicate data (e.g., repeated participant sample). For studies that included the same participant sample, the study that provided the data necessary to compute an effect size was used first. If both articles met that criterion, the article that was published first was included in analysis.
4. Case series ($n < 5$)
5. Ability to calculate effect sizes from reported findings

**Unpublished Data**

To reduce the effects of publication bias on our estimates of effect sizes, we collected unpublished data using the same inclusion and exclusion criteria. Unpublished data were collected through the following methods: unpublished dissertation/thesis databases, contacting individual research labs or researchers involved in PTSD research, and list-serve postings. A literature search was performed under the Global

Dissertation/Thesis database for any unpublished studies that fit the inclusion criteria. Prominent authors who appear regularly among the published articles were contacted and asked for possible unpublished data. Lastly, requests for unpublished data were posted to professional organization list-serves including the Association for Behavioral and Cognitive Therapies and the Anxiety and Depression Association of America.

**Variables**

Measures of PTSD and RSA served as the variables of interest in this meta-analysis. The following RSA measures were included in analysis: SDNN, RMSSD, pNN50, RSA, and HF-HRV. For the purpose of our meta-analysis the only HRV measures that were excluded from coding were very-low frequency HRV, low-frequency HRV, high frequency percentage (the percent of high-frequency bands over total bands), and the low-frequency to high-frequency HRV ratio. These measures were excluded because they include SNS information alongside PSNS information, and therefore, were not exclusively linked to the PSNS (Heathers, 2007). There are also many measures of PTSD, as described above. For this meta-analysis we included any measure that assesses DSM-defined PTSD symptoms. It should be noted that, at final analysis of included articles, there were 15 different measures for assessing PTSD.

**Study Coding Procedures**

A comprehensive study coding spreadsheet was created to collect data across domains within included studies. The coding spreadsheet included basic study information (e.g., authors, year, whether data was published; sample characteristics (e.g., sample size, age, ethnicity, gender, trauma type, population type, cardiovascular disease,

smoking, medication, comorbid disorders); study methods and procedures (e.g., whether the PTSD measure was self-report or structured clinical interview, specific PTSD questionnaire or interview measure used, measure of RSA, type of control group). The coding spreadsheet also included information as to whether the authors needed to be contacted for additional information in order to compute an appropriate effect size based on the data (e.g., baseline RSA not reported; zero-order correlation not reported). Several studies reported multiple measures of RSA (i.e., SDNN, RMSSD, high-frequency HRV) or included multiple control groups (e.g., healthy control, trauma exposed control, other disorder). In these circumstances, each respective RSA measure or control group had a separate effect size coded. In circumstances where multiple effect sizes were computed for several independent subgroups of a study, a weighted average effect size was computed that accounted for larger and smaller subgroups. In circumstances where multiple effect sizes were computed for multiple measures, as in non-independent samples, an average effect size was computed across all measures in which an effect sizes were calculated. A second coder (Dr. Blair Wisco) also coded the effect sizes for each study, and all discrepancies were resolved by consensus.

**Data Analysis**

Hedges's g was selected as the desired effect size to be calculated in this meta-analysis. Hedges's *g* was selected because it provides a better estimate of the standardized mean difference in small samples, as opposed to Cohen's d which can overestimate the effect size. Several of our studies had small samples sizes, leading to the decision to use Hedges's g for the effect size measure.

Due to the variability in the data provided, effect sizes were computed two different ways. For studies that provided independent group means, standard deviations, and samples sizes, the effect size was computed as follows:

$$g = \frac{\bar{x}_1 - \bar{x}_2}{s^*}$$

Where s* is the pooled standard deviation computed as:

$$s^* = \frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2}$$

When studies provided a zero-order correlation between baseline RSA and PTSD, this r-coefficient was then converted into Hedges's g and used as the study effect size. As mentioned before, several studies will have multiple effect sizes calculated due to having more than one RSA measure or more than one control group. When this occurred we used the Comprehensive Meta-Analysis (CMA) software to calculate a pooled effect size. A random effects model was used in the meta-analysis. The random effects model assumes error is systematic, and there is no one true effect size, but rather a population distribution of effect sizes which observed effects are drawn from (Cooper, 2010). In psychological research, random-effects models are utilized more often than fixed-effects models, where variance in the effect size is a result of sampling error alone, due to theory that error varies systematically across studies.

Moderator analyses investigated whether age, gender, type of control group, trauma type, PTSD measure, and RSA measure act as moderators in the association between PTSD and RSA. Each study was coded to include each of these variables and we ran moderator analyses in CMA to determine each moderator's significance. Categorical moderators were assessed in an approach similar to ANOVA, and continuous moderators were assessed in an approach similar to regression (Card, 2015). CMA allowed the target variables to be set as moderator variables at the data entry level, and then select specific levels of each variable at the analyses level. The categorical moderators we examined were the type of control group (i.e., healthy control, trauma exposed control, other mental health control), trauma type (i.e., combat, interpersonal, mixed), PTSD measure (i.e., clinical interview, self-report), and RSA measure (i.e., time-domain, frequency-domain, combined). The moderator analysis produced an effect size and 95% confidence interval at each level of each moderator variable, which allowed us to examine whether specific levels of these moderator variables were significantly different from each other. The continuous moderators examined were mean age of the sample and percent female of the sample (i.e., gender). These variables were run using meta-regression software in CMA. Each continuous moderator was run in a separate model where the variable was entered as a covariate for the overall effect size. The meta-regression produced a coefficient value, standard error, 95% confidence interval, and 2-sided *p*-value for each moderator test.

Publication bias analyses were also run to investigate whether bias existed in the studies included in the meta-analysis. For this evaluation of bias to be thorough, we ran

several analyses. First, we used a funnel plot diagram to examine potential publication bias. We also ran trim and fill analyses (Duval & Tweedie, 2000) and Egger's test (Egger et al., 1997) as secondary analyses. The trim and fill analyses reconstruct the funnel plot diagram to create a more symmetric distribution, by trimming studies with more extreme effect sizes, and/or filling missing studies in order to have symmetry. This analysis then recomputed the effect size with the new data accounting for studies that have either been removed or added. Egger's test is a linear regression where the standard normal deviate is regressed on precision (i.e., the opposite of standard error). The test produces an intercept that relates to the slope of the effect size on standard error. The further the intercept lies from zero, the larger the bias and greater evidence for small-study effects (Sterne et al., 2000). Egger's test is more sensitive to small study effects, and therefore a valid test for publication bias.

# CHAPTER III

# RESULTS

The 50 studies included in the meta-analysis were published or data was collected between 2000 and 2016 and consisted of a total sample of 8045 participants.

## Excluded Studies

The initial keyword search yielded 3,822 articles. All articles retrieved from this search were then merged into Zotero, a reference management program, removing duplicate articles. The next step was to screen articles based on their titles to evaluate whether they were to be included in full-text review. This step yielded 233 articles to be included for full-text review. Using our a priori article inclusion and exclusion criteria, the final number of studies included in the meta-analysis was 50 (Figure 1). It should be noted that an additional 26 studies met inclusion criteria; however, the articles did not include the information needed to compute an accurate effect size. The corresponding authors for these articles were contacted, and either did not respond to our inquiries or were unable to provide the requested information. Eight studies came from unpublished datasets generously provided by colleagues in the field.

## Characteristics of the Studies Included

The studies were quite heterogeneous, as many of the studies' primary research question was not to investigate the association between PTSD and RSA. Of the studies included, there were a mix of treatment outcome and group difference studies. The

majority of studies included involved a mixed trauma type and an adult, community-based sample. Table 1 provides a detailed description of all studies included and their characteristics.

**Effect Size and Moderator Effect Sizes**

The random effects model yielded a small but significant effect size ($g$ = -0.22; 95% CI = -0.32, -0.14; $p < 0.001$) for the association between RSA and PTSD. The effect size was interpreted with the standard Hedges's g cut-points of 0.2 as small, 0.5 as medium, and 0.8 as large. Studies' effect sizes ranged from -0.98 to 0.54, with 14 of the 50 studies indicating significant effect sizes at $\alpha = .05$. The overall heterogeneity measure indicated significant moderate heterogeneity among studies ($I^2 = 51.73$; $p < 0.001$). Thresholds for $I^2$ can be interpreted as 0-40 suggesting non-relevant heterogeneity, 30-60 suggesting moderate heterogeneity, 50-90 suggesting substantial heterogeneity, and 75-100 suggesting considerable heterogeneity. Moderator analyses were run for the following variables: control group, trauma type, PTSD measure, RSA measure, age, and gender. No significant differences were found among these moderator variables (Table 2).

For the categorical moderators, the type of control group moderator yielded healthy control ($g$ = -0.34; 95% CI = -0.51, -0.16), trauma exposed control ($g$ = -0.14; 95% CI = -0.34, 0.06), and other mental health control ($g$= -0.31; 95% CI = -0.59, -0.12). Contrary to our hypothesis that there would be a larger effect among healthy controls than trauma exposed controls or other mental health controls, we did not find a significant effect. Trauma type yielded no significant differences across combat ($g$ = -

0.25; 95% CI = -0.37, -0.13), interpersonal (*g* = -0.37; 95% CI = -0.70, -0.04), and mixed (*g* = -0.31; 95% CI = -0.39, -0.22).

PTSD measure was dichotomized between clinical interview and self-report, and within those categories there were 15 specific measures identified. The clinical interview measures used were the Clinician Administered PTSD Scale (CAPS) (n = 20), and the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorder-IV (DSM-IV) PTSD module (n = 9), International Classification of Diseases (ICD-9) PTSD module (n = 1), Research Diagnostic Interview for Psychological Disorders (F-DIPS) (n = 1), Childhood Trauma Interview (CTI) (n = 1). The rest of the PTSD measures were self-report and included the PTSD Checklist (PCL) (n = 5), Davidson Trauma Scale (DTS) (n = 2), Youth Symptom Survey Checklist (YSSC) (n = 1), PTSD Symptom Scale (PSS) (n = 1), Child PTSD Symptom Scale (CPSS) (n = 1), Trauma Symptom Checklist for Children (TSCC-A) (n = 1), Minnesota Multiphasic Personality Inventory (MMPI-PTSD) PTSD module (n = 1), Detailed Assessment of Posttraumatic Stress (DAPS) (n = 1), Harvard Trauma Questionnaire (HTQ) (n = 1), and Youth Self Report (YSR-PTSD) PTSD module (n = 1). The PTSD measure analysis yielded no significant differences between clinical interview (*g* = -0.25; 95% CI = -0.42, -0.13) and self-report (*g* = -0.22; 95% CI = -0.50, -0.14).

RSA measure yielded the same null results as PTSD measure with no differences between time-domain (*g* = -0.23; 95% CI = -0.41, -0.03), frequency-domain (*g* = -0.20; 95% CI = -0.26, -0.14), and combined (*g* = -0.22; 95% CI = -0.27, -0.17). For the continuous moderators, mean age was not significant (β = -0.01; 95% CI = -0.01, 0.001),

and percent female was also a null finding (β = 0.00; 95% CI = 0.00, 0.003). The age finding was discordant with our hypothesis that age would have a significant effect on effect size.

**Publication Bias**

Several publication bias analyses were run to evaluate whether publication bias may have impacted our findings. First, we graphed a funnel plot of standard error by Hedges's g (Figure 2). The plot yielded a mostly symmetric distribution. Second, we ran Egger's regression test, showing limited publication bias (*b* = -0.13; 95% CI = -1.03, 0.76), with a slope (*b*) near zero indicating low publication bias. As mentioned before, this test was particularly valid for the meta-analysis due to its sensitivity in detecting bias in small studies. Many of our studies had small sample sizes and therefore could have skewed the effect size. However, Egger's regression indicated little publication bias, even among the smaller studies. We ran Duval and Tweedie's trim and fill, also showing limited publication bias (*g* = -0.22; 1 adjusted value filled; 95% CI = -0.31, -0.13), with the reconstructed Hedges's g being identical to original Hedges's g found, and with a low number of adjusted values, indicating no need to adjust the Hedges's g because of significant publication bias. Finally, we ran a moderator analysis between published (*g* = -.26; 95% CI = -0.36, -0.16) and unpublished (*g* = -0.07; 95% CI = -0.23, 0.09) studies, indicating a noticeable difference in effect sizes, despite overlapping confidence intervals.

# CHAPTER IV

# DISCUSSION

This meta-analysis of 50 studies found a small but significant association between PTSD and RSA. This finding provides clarity to the mixed results in the literature and indicates that a reliable association exists. It is possible that the studies which did not report significant findings may have been underpowered to detect an effect of this size, leading to mixed findings in the literature. However, the effect size should be interpreted cautiously due to the effect size's moderate heterogeneity. The heterogeneity of the found effect size was significant, but the sources of that heterogeneity could not be explained by the moderators examined in this meta-analysis.

We expected to find a larger effect size when comparing healthy controls to PTSD participants, as opposed to comparing other control groups (e.g. trauma-exposed controls, other mental health controls) to PTSD participants. However, we did not find a difference among control groups, suggesting there may not be a large difference in RSA among these groups. We also predicted there would be a larger effect size in younger samples than adult samples, but found no evidence of a difference among age groups. This finding again suggests there may not be a substantial difference in the context of age. The other more exploratory moderator analyses also resulted in null findings,

suggesting variables like PTSD measure, RSA measure, or gender may not affect the association between PTSD and RSA. This may mean that when conducting research examining these variables it may not matter how PTSD or RSA are operationalized, or how evenly distributed gender is in the sample.

**Comparisons with Other Meta-Analyses**

First it should be noted the found effect size was similar to a meta-analysis examining cardiac vagal control in depression, with an effect of $d = .33$ (an equivalent Hedges's $g$) (Rottenberg, 2007), suggesting RSA having a similar association across other internalizing disorders. The only other meta-analysis that also investigated the association between RSA and PTSD was conducted approximately three years ago (Nagpal et al., 2013). Nagpal and colleagues (2013) had a wider scope than our study, examining heart rate and low-frequency heart rate variability, alongside parasympathetic activity. However, their meta-analysis was limited by a smaller sample size (n=491, compared with n=8045 in our meta-analysis) and smaller number of studies (n=19, compared with n=50 in our meta-analysis) analyzed due to inclusion criteria. Their meta-analysis only included studies with a control group, excluding correlational data. They also did not include unpublished data in their analyses. Our meta-analysis sought to expand upon their parasympathetic work by extending study inclusion criteria to correlational studies, incorporating unpublished data into our results, and including studies that have been published in the three years between meta-analyses.

Comparing our results to those of the prior meta-analysis is complicated because Nagpal (2013) computed separate effect sizes for each kind of RSA measure, and did not

compute an overall effect size. In their meta-analysis, effect size measures examining RSA ranged from a Hedges's g of -.61 to -2.94 (Nagpal et al., 2013). Their findings show a much larger effect than our results. However, this difference may be attributed to the smaller number of studies, the design of studies included, or the lack of unpublished data in their analysis.

**Publication Bias**

With any meta-analysis, publication bias can threaten the validity of the results. Because of this, it was essential for our analysis to include unpublished data. It is possible that published articles included were systematically different from the unpublished data. Borenstein et al. (2009) notes that significant results are more likely to be published, and published studies are more likely to be included in meta-analyses. Eight unpublished studies or datasets were included in analyses in order to avoid the problem of publication bias. Additionally, several tests to examine the level of publication bias in the literature were conducted. First, the moderator analysis between published and unpublished studies indicated a substantial, albeit nonsignificant, difference in effect sizes. The finding suggests possible publication bias because the published study effect size is much larger. The funnel plot of standard error by Hedges's g yielded a mostly symmetric distribution. The more symmetric the distribution the less bias in the studies included. Second, Egger's regression test revealed a slope near zero, indicating low publication bias. Lastly, we ran Duval and Tweedie's trim and fill, also showing limited publication bias, with only one adjusted value added to the study distribution, and an identical Hedges's g as we found previously.

All publication bias tests except the moderator analysis indicated little bias in our results, exhibiting a strength in this meta-analysis. However, it is still worthwhile to consider motives of publication bias in the literature. The "file drawer effect" is a common problem in the literature, with significant findings being much more common to be published than null findings. We attempted to target this problem by including unpublished findings; however, the number of published studies (n=42) outnumbered unpublished data (n=8). It is possible that the "file drawer effect" was not as strong in our analyses because of the nature of the published studies included. A number of published studies were not examining the association between RSA and PTSD as their primary outcome. Many studies included were treatment studies, or studies primarily examining other variables associated with PTSD (e.g., sleep, aggression, attention bias, marital health) that happened to include a measure of RSA. These studies, whose primary outcome was not RSA, are less likely to be influenced by the "file drawer effect," leading to less publication bias in studies included in our meta-analysis.

**Limitations**

This meta-analysis had limitations both general to all meta-analyses, as well as unique to this specific design. First, many studies did not have clean samples and did not exclude participants for variables like medication, smoking, and medical conditions. Pole's meta-analysis (2007) found no moderation between psychoactive medications and psychophysiological effects, although he did not examine RSA. However, the field tends to exclude psychoactive medications when examining physiological variables to reduce heterogeneity. The studies included in our meta-analysis included participants using

psychoactive medications, along with participants who were free of these medications, potentially impacting our findings. Smoking has also been found to blunt vagal modulation (Barutcu et al., 2005) and therefore may have confounded results. Finally, medical conditions including cardiovascular disease were not always accounted for in included studies, which would lead to decreased RSA independent of psychopathology (Thayer et al., 2009). We initially hoped to include these variables in our moderator analyses, but upon coding the studies included, a significant portion of the studies analyzed had missing information about these variables.

A second limitation in this meta-analysis was the exclusion of 26 studies because authors did not respond to inquiries related to computing an accurate effect size. Several studies did not provide baseline data or bivariate correlations in the published articles. The corresponding authors were each contacted three times before excluding the article due to non-response. This affected overall power, along with power to detect significant moderators. It is possible the moderators of type of control group and trauma type could have displayed significance if each level had been adequately powered.

**Future Directions**

Our findings have provided some answers to the relationship between PTSD and RSA; however, there are still many questions to be answered. Due to the heterogeneity of our results and the null findings with the moderator variables examined, it is important to consider other possible moderators of this association. Specifically, it may be advantageous to examine sample exclusion criteria (e.g. smoking status, medication, medical conditions) more closely and see if these variables explain any heterogeneity.

Additionally, with greater power studies can further examine specific trauma types. In order to examine this variable, it will be necessary for studies to recruit specific trauma types instead of a mixed trauma sample that was commonly used in the studies we examined.

Our main finding indicates that RSA and PTSD are correlated, clearing up the past ambiguity of this association due to a mixed literature. This finding cannot determine whether low RSA is a risk factor for developing PTSD or if low RSA is a result of PTSD. However, if low RSA were to be a risk factor, practitioners would likely want to target this physiological abnormality by implementing simple interventions like increasing exercise or decreasing smoking in order to increase RSA. If low RSA is a result of PTSD, practitioners may want to instead encourage evidence-based psychological interventions to treat the mental disorder, in the hopes of RSA increasing as the PTSD symptoms dissipate.

Our finding can be broadened to suggest there is a connection between mental and physical health. This connection has significant implications in clinical settings where there has been a push toward integrative care. RSA could be utilized by both medical doctors and mental health providers as a tool to track physical health progress alongside client self-reports. This finding may also suggest that as people with PTSD are treated for the disorder, as their PTSD symptoms decrease their RSA may increase, suggesting both mental and physical health benefits.

This finding also has beneficial research implications. RSA may now be more consistently measured when examining physiological responses in PTSD samples. This

may allow for future research to uncover how RSA may change across established evidence based treatments or in more novel therapeutic approaches. Researchers will also be able to examine RSA in relation to other known symptoms of PTSD (e.g., flashbacks, nightmares, negative cognitions, avoidance) and see how RSA relates to specific re-experiencing symptoms, as opposed to negative cognitions or avoidance. Finally, as the literature continues to grow, it will be necessary to conduct further moderator analyses with adequate power to best explain the heterogeneity of the effect size.

Overall, our meta-analysis provides clarity to the mixed literature surrounding the association between RSA and PTSD. This significant association reinforces the increased need to examine physiological measures in psychological research in the hopes of better understanding the physiological effects of mental illness.

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# APPENDIX A

## TABLES AND FIGURES

Table 1. Characteristics of Studies Included in Meta-analysis

| First Author | Year | Sample Size | Categorical vs Continuous | Number of Control Groups | Average Age | Percent Female | Trauma Type | Control Group(s) | RSA Measure | PTSD Measure | Publication Status |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Agorastos | 2013 | 15 | Categorical | 1 | 28.7 | 0 | Combat | Trauma-Exposed Control | Combined | Clinical Interview | Published |
| Cohen | 2000 | 64 | Categorical | 2 | 34.14 | 60 | Mixed | Healthy Control, Other Mental Health Control | Frequency | Clinical Interview | Published |
| D'Andrea | 2012 | 20 | Correlational | 0 | 38 | 100 | Mixed | Not Applicable | Frequency | Self-Report | Published |
| Dennis | 2014 | 227 | Categorical | 1 | 29.32 | 57 | Mixed | Not Specified | Frequency | Clinical Interview | Published |
| DePierro | 2013 | 27 | Correlational | 0 | 27.5 | 100 | Mixed | Not Applicable | Frequency | Self-Report | Published |
| Eonta | 2013 | 218 | Correlational | 0 | 21.5 | 72 | Mixed | Not | Frequency | Self- | Unpublished |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Applicable | | Report | |
| Barry | 2015 | 147 | Correlational | 0 | 19.02 | 53 | Mixed | Not Applicable | Frequency | Self-Report | Published |
| Hauschildt | 2011 | 44 | Categorical | 1 | 35.11 | 75 | Interpersonal | Healthy Control | Combined | Clinical Interview | Published |
| Jovanovic | 2009 | 78 | Categorical | 1 | 39.38 | 0 | Combat | Healthy Control | Frequency | Clinical Interview | Published |
| Kamkwalala | 2012 | 141 | Categorical | 1 | 39.80 | 61 | Mixed | Trauma Exposed Control | Frequency | Self-Report | Published |
| Bertram | 2014 | 46 | Categorical | 1 | 54.16 | 0 | Mixed | Healthy Control | Frequency | Clinical-Interview | Published |
| Fainsilber | 2015 | 75 | Correlational | 0 | 9.33 | 51 | Not Specified | Not Applicable | Frequency | Self-Report | Published |
| Keary | 2009 | 40 | Categorical | 1 | 37.75 | 100 | Mixed | Healthy Control | Frequency | Clinical Interview | Published |
| Kirsch | 2015 | 34 | Categorical | 1 | 12.90 | 63 | Mixed | Trauma Exposed Control | Frequency | Clinical Interview | Published |
| Kobayashi | 2014 | 37 | Categorical | 1 | 23.05 | 68 | Mixed | Trauma Exposed Control | Frequency | Clinical Interview | Published |
| Lakusic | 2007 | 68 | Categorical | 1 | 49.0 | 0 | Combat | Healthy Control | Combined | Clinical Interview | Published |
| Lee | 2012 | 125 | Categorical | 1 | 48.22 | 100 | Mixed | Healthy | Time | Clinical | Published |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Control | | Interview | |
| Lewis | 2015 | 848 | Correlational | 0 | 23.82 | 4.50 | Not Specified | Not Applicable | Frequency | Self-Report | Published |
| MacArthur | 2011 | 61 | Correlational | 0 | 15.70 | 44.30 | Mixed | Not Applicable | Time | Self-Report | Unpublished |
| Minassian | 2014 | 2430 | Categorical | 2 | 22.80 | 0 | Combat | Healthy Control, Other Mental Health Control | Frequency | Clinical Interview | Published |
| Minassian | 2015 | 745 | Categorical | 1 | 22.40 | Not Specified | Not Specified | Healthy Control | Frequency | Clinical Interview | Published |
| Moon | 2013 | 51 | Categorical | 1 | 37.21 | 62.00 | Mixed | Healthy Control | Combined | Clinical Interview | Published |
| Murray | 2012 | 87 | Categorical | 1 | 21.70 | 0 | Not Specified | Healthy Control | Combined | Clinical Interview | Unpublished |
| Muse | 2013 | 66 | Correlational | 0 | 36.02 | 0 | Not Specified | Not Applicable | Time | Self-Report | Unpublished |
| Blechert | 2007 | 81 | Categorical | 2 | 41.92 | 71.62 | Mixed | Healthy Control, Other Mental Health Control | Frequency | Clinical Interview | Published |
| Sahar | 2001 | 29 | Categorical | 1 | 41.75 | 0 | Mixed | Trauma Exposed | Frequency | Clinical Interview | Published |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Control | | | |
| Schecter | 2011 | 54 | Categorical | 2 | 30.68 | 100 | Interpersonal | Trauma Exposed Control, Other Mental Health Control | Frequency | Clinical Interview | Published |
| Brady | 2015 | 115 | Correlational | 0 | 32.90 | 9.70 | Combat | Not Applicable | Combined | Clinical Interview | Published |
| Shah | 2013 | 459 | Categorical | 2 | 55.15 | 0 | Combat | Healthy Control, Other Mental Health Control | Frequency | Clinical Interview | Published |
| Shaikh al arab | 2012 | 21 | Categorical | 1 | 24.50 | Not Specified | Traffic Accident | Trauma Exposed Control | Time | Clinical Interview | Published |
| Shenk | 2012 | 110 | Correlational | 0 | 17.00 | 100 | Interpersonal | Not Applicable | Frequency | Clinical Interview | Published |
| Slewa-Younan | 2012 | 25 | Categorical | 0 | Not Specified | 48.12 | Mixed | Other Mental Health Control | Frequency | Clinical Interview | Published |
| Song | 2011 | 24 | Categorical | 1 | 50.20 | 71.90 | Mixed | Trauma Exposed Control | Combined | Self-Report | Published |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Tan | 2009 | 28 | Correlational | 0 | 31.68 | 7.1 | Combat | Not Applicable | Time | Clinical Interview | Published |
| Tucker | 2012 | 64 | Categorical | 2 | 37.6 | Not Specified | Hurricane Katrina | Healthy Control, Trauma Exposed Control | Frequency | Clinical Interview | Published |
| Buss | 2011 | 62 | Correlational | 0 | 38.19 | 64.5 | Mixed | Not Applicable | Time | Clinical Interview | Unpublished |
| Wahbeh | 2013 | 81 | Categorical | 1 | 53.90 | 0 | Combat | Trauma Exposed Control | Frequency | Clinical Interview | Published |
| Wahbeh | 2013 | 45 | Categorical | 2 | Not Specified | Not Specified | Combat | Healthy Control, Trauma Exposed Control | Frequency | Clinical Interview | Published |
| Woodward | 2008 | 77 | Categorical | 1 | 49.00 | 8.0 | Combat | Trauma Exposed Control | Frequency | Clinical Interview | Published |
| Woodward | 2009 | 48 | Categorical | 2 | 42.00 | Not Specified | Mixed | Healthy Control, Other Mental Health Control | Frequency | Clinical Interview | Published |
| Dennis | 2016 | 167 | Correlational | 1 | 29.78 | 48.00 | Mixed | Healthy Control | Frequency | Self-Report | Published |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Green | 2016 | 83 | Correlational | 0 | 30.19 | 57.00 | Mixed | Not Applicable | Frequency | Self-Report | Published |
| Liddell | 2016 | 80 | Correlational | 0 | 39.00 | 62.00 | Mixed | Not Applicable | Time | Self-Report | Published |
| McLaughlin | 2013 | 168 | Correlational | 0 | 14.90 | 56.00 | Mixed | Not Applicable | Frequency | Self-Report | Published |
| Meyer | 2016 | 68 | Categorical | 2 | 31.29 | Not Specified | Mixed | Healthy Control, Other Mental Health Control | Combined | Clinical Interview | Published |
| Kobayashi | 2016 | 71 | Categorical | 1 | 22.75 | 59.49 | Mixed | Trauma Exposed Control | Frequency | Clinical Interview | Published |
| Wisco | 2015 | 10 | Categorical | 1 | 29.00 | 80.00 | Mixed | Trauma Exposed Control | Frequency | Clinical Interview | Unpublished |
| Wisco | 2015 | 56 | Correlational | 0 | 54.04 | 3.60 | Mixed | Not Applicable | Frequency | Clinical Interview | Unpublished |
| Liverant | 2016 | 79 | Categorical | 1 | 51.17 | 12.50 | Mixed | Other Mental Health Control | Frequency | Clinical Interview | Unpublished |
| Chang | 2013 | 256 | Categorical | 2 | 36.79 | 41.00 | Mixed | Healthy Control, Trauma Exposed | Frequency | Self-Report | Published |

Control

Table 2. Moderator Analyses

| Categorical Moderators | N | Hedges's g | 95% CI | |
|---|---|---|---|---|
| Control Group | | | | |
| Healthy Control | 18 | -0.34 | -0.51, -0.16 | |
| Trauma Exposed Control | 15 | -0.14 | -0.34, 0.06 | |
| Other Mental Health Control | 9 | -0.31 | -0.59, -0.12 | |
| Trauma Type | | | | |
| Combat | 11 | -0.25 | -0.37, -0.13 | |
| Interpersonal | 4 | -0.22 | -0.64, 0.20 | |
| Mixed | 29 | -0.31 | -0.39, -0.22 | |
| RSA Measure | | | | |
| Time | 7 | -0.23 | -.41, -0.03 | |
| Frequency | 34 | -0.20 | -0.26, -0.14 | |
| Combined | 9 | -0.22 | -0.27, -0.17 | |
| PTSD Measure | | | | |
| Clinical Interview | 35 | -0.25 | -0.42, -0.13 | |
| Self-Report | 15 | -0.22 | -0.50, -0.14 | |
| Continuous Moderators | N | β | 95% CI | p |
| Age | 43 | -0.01 | -0.01, 0.001 | 0.08 |
| Gender | 29 | 0.00 | 0.00, 0.003 | 0.99 |

Categorical moderator significance is found if confidence intervals are nonoverlapping. Continuous moderator significance is found if $p < 0.05$.
*N's do not always sum up to total of 50 studies due to some studies not providing necessary moderator information to run analyses.
*Raw beta weights provided.

Figure 1. Article Inclusion PRISMA Flow Diagram

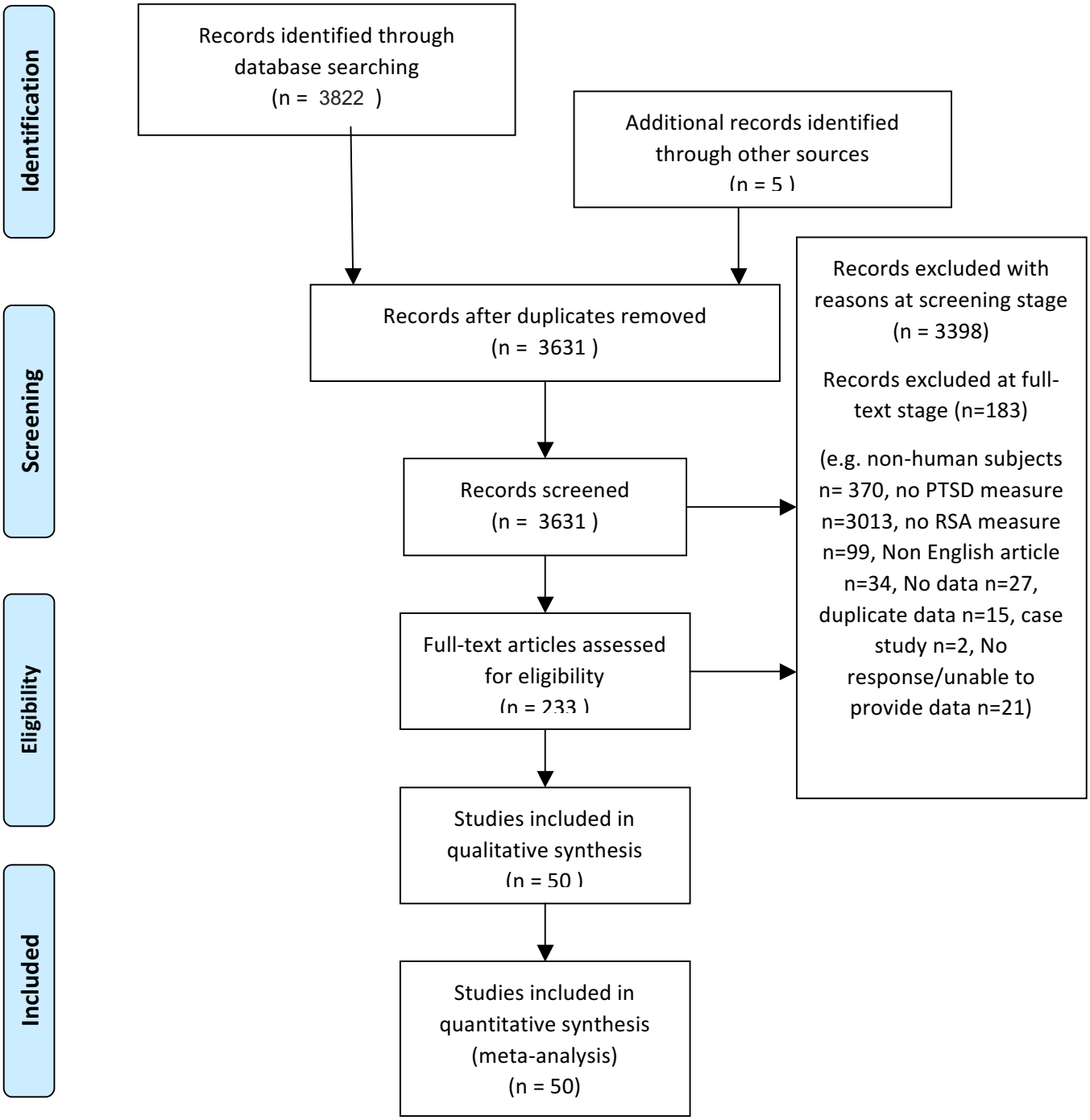
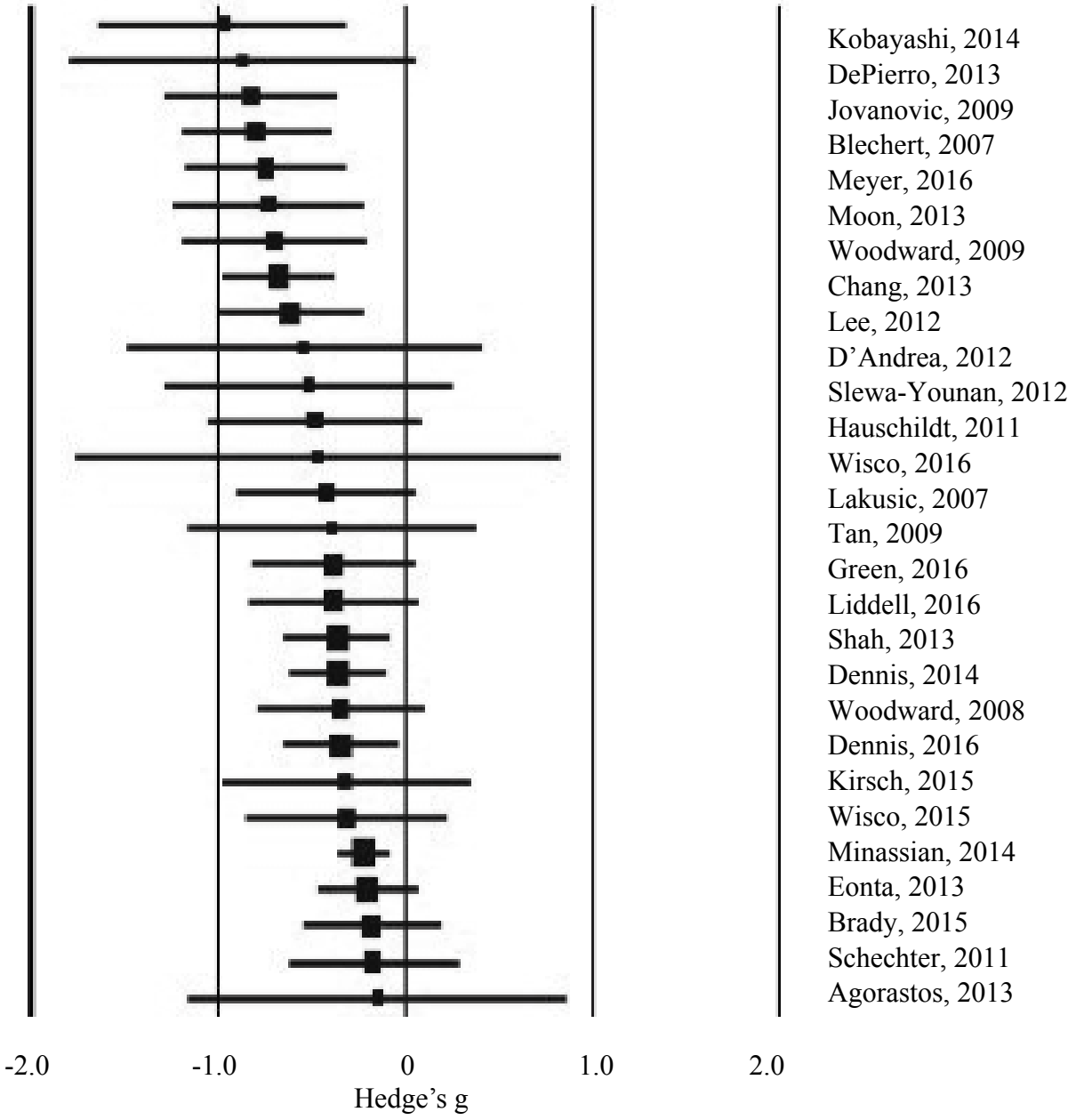


Figure 2. Forrest Plot of all Studies Included in Meta-analysis.

*Studies are sorted from smallest to largest effect size. The size of the square reflects the sample size, with larger squares indicative of larger samples.



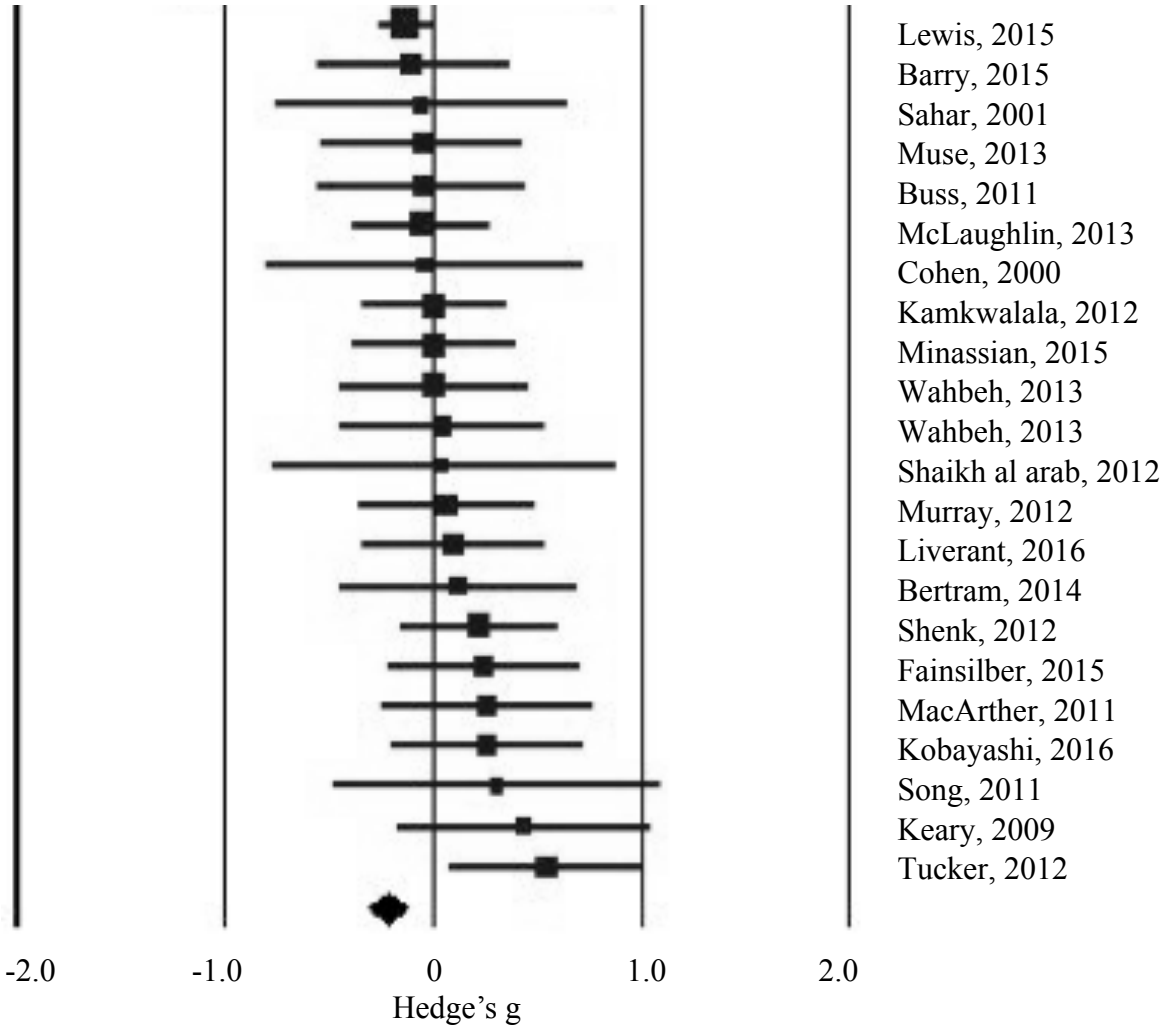
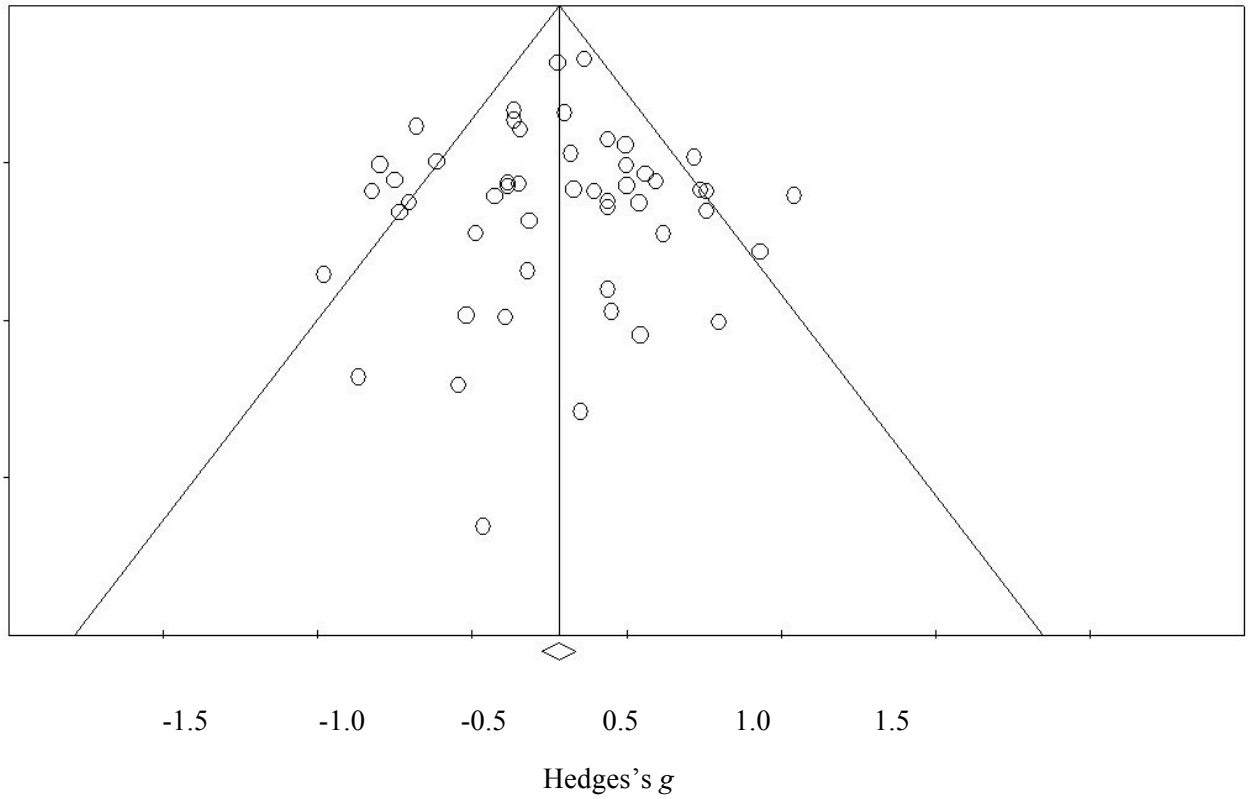

Lewis, 2015
Barry, 2015
Sahar, 2001
Muse, 2013
Buss, 2011
McLaughlin, 2013
Cohen, 2000
Kamkwalala, 2012
Minassian, 2015
Wahbeh, 2013
Wahbeh, 2013
Shaikh al arab, 2012
Murray, 2012
Liverant, 2016
Bertram, 2014
Shenk, 2012
Fainsilber, 2015
MacArther, 2011
Kobayashi, 2016
Song, 2011
Keary, 2009
Tucker, 2012
-2.0
-1.0
0
1.0
2.0
Hedge's g

Figure 3. Funnel Plot of Publication Bias




This figure illustrates where individual study effect sizes fall. The more symmetrical the funnel plot, the less publication bias present.