Patterns and Mediators of Emotion Regulatory Disturbance in Panic Disorder

BY

CASEY SARAPAS
B.S., Fordham University, 2007
M.A., University of Illinois at Chicago, 2011

THESIS

Submitted as partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Psychology (Clinical Psychology)
in the Graduate College of the
University of Illinois at Chicago, 2016

Chicago, Illinois

Defense Committee:

Stewart Shankman, Chair and Advisor
Evelyn Behar
Scott Langenecker
Heide Klumpp, Psychiatry
Jutta Joormann, Yale University
This thesis is dedicated to my mother, Patricia Eleanor Crafts, who first sparked my love of learning. Her selflessness, perseverance, humility, and humor provide an example I strive to emulate in my professional and personal lives.
ACKNOWLEDGMENTS

I thank Lynne Lieberman, Huiting Liu, and Elizabeth Stevens for their dedicated assistance in collecting data for this study, and Dae Kim for assistance in data processing. Scott Langenecker and Anna Weinberg provided much-appreciated consultation on task design and physiological data processing, respectively. Special thanks to my friend and mentor Stewart Shankman, who provided invaluable consultation and support throughout all phases of this research.

This study was supported by National Institute of Mental Health grant F31 MH100823.

CS
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>CHAPTER</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>1.1 Emotion Regulation in Panic Disorder: Too Little or Too Much?</td>
<td>2</td>
</tr>
<tr>
<td>1.2 Emotion Regulation in Agoraphobia</td>
<td>5</td>
</tr>
<tr>
<td>1.3 Methodological Challenges in Studying Emotion Regulation</td>
<td>6</td>
</tr>
<tr>
<td>1.3.1 Limitations of Self-Report and a Potential Solution</td>
<td>6</td>
</tr>
<tr>
<td>1.3.2 Startle and Corrugator: Assessing Related but Distinct Affective Processes</td>
<td>8</td>
</tr>
<tr>
<td>1.3.3 Prior Studies</td>
<td>9</td>
</tr>
<tr>
<td>1.4 Effortful Control as a Mechanism of Emotion Regulation</td>
<td>10</td>
</tr>
<tr>
<td>1.5 Aims and Hypotheses</td>
<td>12</td>
</tr>
</tbody>
</table>

| 2. METHOD | 14 |
| 2.1 Participants | 14 |
| 2.1.1 Enrollment Criteria | 14 |
| 2.1.2 Participant Flow | 15 |
| 2.2 Psychopathology Measures | 15 |
| 2.2.1 Diagnostic Interviews | 15 |
| 2.2.2 Panic Disorder Severity | 15 |
| 2.3 Procedure | 16 |
| 2.3.1 Shock Work-Up | 16 |
| 2.3.2 Emotion Regulation Task | 17 |
| 2.3.2.1 Task Procedures | 17 |
| 2.3.2.2 Dependent Measures | 18 |
| 2.3.3 Effortful Control Tasks | 19 |
| 2.3.3.1 Parametric Go/No-Go/Stop Task | 20 |
| 2.3.3.2 Attention Network Test – Short Version | 21 |
| 2.4 Physiological Data Processing | 22 |
| 2.5 Data Analysis | 22 |
| 2.5.1 Missing Data | 22 |
| 2.5.2 Evaluation of Covariates | 23 |
| 2.5.3 Task Effects | 23 |
| 2.5.4 Emotion Regulation | 23 |
| 2.5.5 Effortful Control | 24 |
| 2.5.6 Relationships of Emotion Regulation with Effortful Control | 24 |

| 3. RESULTS | 25 |
| 3.1 Participants | 25 |
| 3.2 Evaluation of Potential Covariates | 27 |
| 3.3 Basic Task Effects | 27 |
| 3.4 Emotion Regulation Task | 28 |
| 3.5 Effortful Control Tasks | 30 |
| 3.6 Relationships of Emotion Regulation with Effortful Control | 31 |
TABLE OF CONTENTS (continued)

<table>
<thead>
<tr>
<th>CHAPTER</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. DISCUSSION</td>
<td>34</td>
</tr>
<tr>
<td>4.1 Emotion Regulation in Panic Disorder: The Role of Agoraphobia</td>
<td>34</td>
</tr>
<tr>
<td>4.2 Emotion Regulation and Effortful Control</td>
<td>36</td>
</tr>
<tr>
<td>4.3 Divergence and Convergence Across Multiple Measures</td>
<td>38</td>
</tr>
<tr>
<td>4.4 Implications for Treatment</td>
<td>39</td>
</tr>
<tr>
<td>4.5 Strengths and Limitations</td>
<td>40</td>
</tr>
<tr>
<td>4.6 Conclusion</td>
<td>41</td>
</tr>
<tr>
<td>CITED LITERATURE</td>
<td>43</td>
</tr>
<tr>
<td>APPENDIX</td>
<td>61</td>
</tr>
<tr>
<td>VITA</td>
<td>64</td>
</tr>
</tbody>
</table>
## LIST OF TABLES

<table>
<thead>
<tr>
<th>TABLE</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td></td>
</tr>
<tr>
<td>DEMOGRAPHIC AND CLINICAL CHARACTERISTICS</td>
<td>26</td>
</tr>
<tr>
<td>II.</td>
<td></td>
</tr>
<tr>
<td>PEARSON CORRELATIONS AMONG MEASURES OF EMOTION REGULATION AND EFFORTFUL CONTROL</td>
<td>32</td>
</tr>
</tbody>
</table>
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>FIGURE</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Schematic of emotion regulation task</td>
<td>18</td>
</tr>
<tr>
<td>2. Group differences in voluntary emotion regulation</td>
<td>29</td>
</tr>
<tr>
<td>3. Group differences in attentional control</td>
<td>31</td>
</tr>
<tr>
<td>4. Relationship between effortful control ability and voluntary emotion regulatory ability</td>
<td>33</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>Analysis of covariance</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>ANT-S</td>
<td>Attention Network Test – Short Version</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>dB</td>
<td>Decibels</td>
</tr>
<tr>
<td>DSM-5</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, 5th Edition</td>
</tr>
<tr>
<td>EMG</td>
<td>Electromyography</td>
</tr>
<tr>
<td>HRV</td>
<td>Heart rate variability</td>
</tr>
<tr>
<td>IDAS</td>
<td>Inventory for Depression and Anxiety Symptoms</td>
</tr>
<tr>
<td>ITI</td>
<td>Intertrial interval</td>
</tr>
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<td>M</td>
<td>Mean</td>
</tr>
<tr>
<td>PD/A</td>
<td>Panic disorder with agoraphobia</td>
</tr>
<tr>
<td>PD/NA</td>
<td>Panic disorder without agoraphobia</td>
</tr>
<tr>
<td>PDSS</td>
<td>Panic Disorder Severity Scale</td>
</tr>
<tr>
<td>PGNGS</td>
<td>Parametric Go/No-Go/Stop task</td>
</tr>
<tr>
<td>RDoC</td>
<td>Research Domain Criteria</td>
</tr>
<tr>
<td>RT</td>
<td>Reaction time</td>
</tr>
<tr>
<td>SCID-5</td>
<td>Structured Clinical Interview for DSM-5</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
</tbody>
</table>
SUMMARY

Emotion dysregulation is an oft-cited and potentially valuable explanation for panic disorder and other anxiety disorders. However, theoretical accounts conflict regarding whether panic disorder is associated with deficient or excessive emotion regulation, and these contradictory predictions have not been resolved by extant, primarily self-report-based studies. The present study (1) attempted to clarify the functioning of emotion regulation in panic disorder and (2) examined a putative mechanism for emotion regulatory dysfunction, effortful control. In a sample of 38 individuals with panic disorder and 37 controls, we gauged participants’ ability to voluntarily regulate emotional responding to unpredictable threat of shock using physiological indices of negative emotion (startle eye-blink reflex and corrugator activity). We also assessed performance on 3 behavioral measures of effortful control; the degree to which these measures were disrupted in a threatening context; and whether effortful control abilities were associated with emotion regulatory ability. Individuals with panic disorder with agoraphobia (PD/A) demonstrated an enhanced ability to voluntarily suppress both startle and corrugator responding to threat relative to controls and panic disorder without agoraphobia (PD/NA). Individuals with PD/NA showed poorer attentional control compared to controls and PD/A. All 3 measures of effortful control were positively correlated with startle suppression ability, and path analyses revealed indirect effects of PD/NA on emotion regulatory ability via attentional control. The results implicate excessive suppression of negative emotion in the maintenance of PD/A and add to a growing literature linking non-emotional effortful cognitive abilities to emotion regulation and psychopathology.
1. INTRODUCTION

Panic disorder is associated with more impairment and higher per-individual annual costs than any other DSM-5 anxiety disorder (Batelaan et al., 2007; Kessler et al., 2005). These economic and functional burdens are especially pronounced for individuals with comorbid agoraphobia (Kessler et al., 2006). Although moderately effective treatments for panic disorder exist, these treatments have substantial rates of attrition and non-response (e.g., Craske et al., 2003; 2007), particularly for agoraphobic individuals (Porter and Chambless, 2015). A better understanding of the basic disturbances that cause and maintain panic and other anxiety disorders is needed to develop more efficacious and tolerable treatments and to refine current treatment approaches (Watkins, 2009).

Abnormalities in emotion regulation are frequently cited as etiological and maintenance factors for problematic anxiety, including panic disorder. However, conflicting theoretical models predict both deficient (e.g., Friedman and Thayer, 1998) and excessive (e.g., Bouton et al., 2001; Cisler et al., 2010) emotion regulation in panic disorder, and empirical findings to date have not clearly ruled out either possibility. These contradictory theories and results may reflect methodological limitations of previous studies, including a reliance on self-report measures of emotion regulation and a lack of attention to heterogeneous subgroups within panic disorder. The construct of effortful control is a proposed mechanism for anxiety-related emotion dysregulation (Lewis et al., 2010), but research has rarely examined whether individual differences in effortful control predict emotion regulation abilities. Moreover, the specific pathways through which effortful control might affect emotion regulation have rarely been explored. For example, difficulties with emotion regulation could reflect stable, baseline deficits in effortful control, or transient disruption of effortful control capacity during stressful situations.
Thus, although the constructs of emotion regulation and effortful control both hold promise for advancing our understanding of panic and other anxiety disorders, their promise has not been fully realized. The present study employed real-time behavioral and psychophysiological measures of emotion regulation and effortful control to investigate how these processes function in panic disorder and interact with one another.

1.1 Emotion Regulation in Panic Disorder: Too Little or Too Much?

Emotion regulation refers to a diverse set of processes and behaviors through which individuals attempt to influence their experience and expression of emotion (Durbin and Shafir, 2008; Gross, 1998; Gross and Thompson, 2007). It is a transdiagnostic construct cited in theoretical models of many mental disorders (e.g., Joormann and Quinn, 2014; Townsend and Altshuler, 2012; Wilcox et al., 2016), including panic disorder and other anxiety disorders (Behar et al., 2009; Cisler et al., 2010; Friedman and Thayer, 1998). As conceptualized by Gross’s process model (1998; Gross and Thompson, 2007), emotion regulation encompasses a broad set of antecedent-focused strategies including situation selection (e.g., behavioral avoidance or escape), situation modification (e.g., carrying a safety object), attentional deployment (e.g., cognitive avoidance or attentional re-orienting), and cognitive change (e.g., reappraisal or denial), as well as the response-focused strategy of response modulation (e.g., suppression of facial expression). Because emotion regulation can be conceptualized as a cognitive ability that acts on emotional processes, it offers a useful framework for integrating research on cognitive and emotional disturbances in anxiety disorders. Research on emotion regulatory ability is also clinically relevant—a deeper understanding of how and why anxious individuals have difficulty regulating emotional responding may lay groundwork for treatments
that better address this difficulty (Allen et al., 2008; Farchione et al., 2012) or point towards improvements to current treatments.

Although many theorists have implicated emotion dysregulation in the etiology or maintenance of panic disorder, they disagree on the nature of this dysregulation. Some theoretical models posit deficient emotion regulation in panic disorder. For instance, Thayer and colleagues’ neurovisceral integration model proposes that panic disorder (Friedman and Thayer, 1998) and other anxiety disorders (Thayer et al., 2012) are associated with impairments in inhibitory control and flexible regulation of autonomic reactivity, indexed by low heart rate variability (HRV). They argue that these deficits result in a failure to inhibit the emotional and physiological expression of maladaptive fear and anxiety, including panic attacks. Similarly, based on imaging studies showing increased frontal activity following cognitive-behavioral therapy for panic disorder (Prasko et al., 2004; Sakai et al., 2006), Shurick and Gross (2013) propose that untreated panic disorder is characterized by deficient prefrontal control of learned fear responses. Some theorists have also conceptualized the attentional bias towards threat cues reported in panic and other anxiety disorders (Pergamin-Hight et al., 2015) as a failure to exercise emotion regulation through attentional redeployment (e.g., Amstadter, 2008; Kring and Werner, 2004; per Gross, 1998). Consistent with these deficient regulation models, individuals with panic disorder report less perceived control over their anxiety (e.g., López et al., 2016) and greater emotion regulatory difficulties (e.g., Tull et al., 2009) than non-anxious individuals.

Other models instead attribute panic disorder to excessive attempts to regulate negative emotion (Bouton et al., 2001; Cisler et al., 2010; Craske and Barlow, 2008). Many studies report that individuals with panic disorder or recurrent panic attacks are less accepting of negative
emotion than controls and more frequently attempt to suppress, avoid, or otherwise control these emotions (Baker et al., 2004; Hino et al., 2002; Katerndahl, 1999; Tull and Roemer, 2007; Tull et al., 2008; Vitaliano et al., 1987; Vollrath and Angst, 1993). Paradoxically, however, experimental studies show that attempts to suppress negative emotion generally produce increased negative affect among individuals with panic disorder (Levitt et al., 2004), other anxiety disorders (Campbell-Sills et al., 2006), or high anxiety sensitivity (Eifert and Heffner, 2003; Feldner et al., 2006). Based on these findings, Cisler and colleagues (2010) proposed a two-process model of maladaptive emotion regulation in anxiety disorders. First, due to paradoxical effects of emotion suppression, individuals predisposed towards excessive suppression of negative emotion are likely to experience greater distress during initial encounters with feared stimuli (e.g., uncomfortable physical sensations). Cisler and colleagues argue that this results in more powerful fear conditioning, leading to increasingly intense fear responses (e.g., panic attacks) and, ultimately, disorder onset. Second, continued attempts to suppress negative emotion following disorder onset lead to chronic elevations in negative emotion (e.g., sustained anxious apprehension about panic attacks) and avoidance (e.g., agoraphobia), which causes the generalized distress and functional impairment characteristic of anxiety disorders.

Following Mowrer’s (1947) classic two-factor theory of fear learning, contemporary learning models emphasize avoidance, rather than suppression, as the primary form of maladaptive emotion regulation in panic disorder. According to these models, behavioral avoidance of feared situations maintains panic disorder by limiting opportunities for extinction or corrective experiences (Bouton et al., 2001; Craske and Barlow, 2008; Mineka and Zinbarg, 2006). More subtle forms of avoidance such as safety behaviors dampen the effects of potentially corrective experiences when they do occur (Lovibond et al., 2009; Salvoskis et al., 1999). These
models also describe avoidance as self-exacerbating: avoidance of panic-related situations is negatively reinforced by short-term relief from fear and anxiety, ultimately leading to agoraphobia for some individuals.

In sum, these theories make contradictory predictions regarding how emotion regulation functions among individuals with panic disorder. Some models predict that these individuals are unable to regulate anxiety and other negative emotions (Friedman and Thayer, 1998; Shurick and Gross, 2013); one model predicts paradoxical increases in negative emotion due to excessive efforts at emotion regulation (Cisler et al., 2010); and some models predict excessive emotion regulatory efforts associated with short-term reductions in negative emotion (but deleterious longer-term consequences; Bouton et al., 2001; Craske and Barlow, 2008).

1.2 Emotion Regulation in Agoraphobia

Research to date has not examined whether panic disorder with agoraphobia (PD/A) and panic disorder without agoraphobia (PD/NA) are associated with different patterns of emotion regulation. However, indirect evidence suggests that individuals with PD/A may be especially likely to engage in excessive regulation of negative emotion. Indeed, agoraphobia itself can be conceptualized as a form of maladaptive emotion regulation (Craske and Barlow, 2008; an example of “situation selection” as described by Gross’s [1998] process model). Although panic disorder has generally been associated with heightened startle responding to threat (Grillon et al., 2008; Shankman et al., 2013), several reports indicate that individuals with PD/A show lower startle reactivity compared to both PD/NA (McTeague et al., 2011) and healthy controls (Cuthbert et al., 2003). Similarly, whereas subclinical anxiety is associated with deficient recruitment of frontal regions during threat processing, hyperreactivity of these regions
has been reported in full-syndrome anxiety disorders, including panic disorder (Hofmann et al., 2012; Reinecke et al., 2015). Reinecke and colleagues (2015) reported that this increased threat-related frontal activation was positively correlated with agoraphobia and panic symptom severity. Considered together, these findings suggest that individuals with PD/A may engage in a higher degree of effortful emotion suppression than those with PD/NA. It is possible that unappreciated differences between these subgroups may have contributed to inconsistent findings regarding emotion regulation in panic disorder.

1.3 **Methodological Challenges in Studying Emotion Regulation**

1.3.1 **Limitations of Self-Report and A Potential Solution**

The lack of consensus regarding the nature of emotion regulation in panic disorder may reflect shortcomings in how this construct has typically been measured. Most studies have asked participants to self-report how easily or effectively they regulate emotions in hypothetical or retrospective situations (Baker et al., 2004; Hino et al., 2002; Katerndahl, 1999; Lopez et al., 2016; Tull and Roemer, 2007; Tull et al., 2008; 2009; Vitaliano et al., 1987; Vollrath and Angst, 1993). There are several problems with this approach. First, self-report is subject to recall bias and demand characteristics, and this may be particularly true for self-report of emotional tendencies (Faith et al., 1998; Robinson and Clore, 2002; Sato and Kawahara, 2012). Indeed, several studies indicate that individuals’ retrospective reports of affect regulation strategy use do not correspond well to real-time, experience sampling measurements of the same (Ptacek, et al., 1994; Stone et al., 1998). Second, humans’ estimates of their own mental abilities are frequently inaccurate (Akbar et al., 2011; Dodrill, 1997; Richardson-Vejlgaard et al., 2009; Seidenberg et al., 1994). Third, self-report measures may confound differences in emotion *regulation* with differences in basic emotional *reactivity* (Campos et al., 2004; Lewis et al., 2010). To avoid
some of these limitations, some researchers have assessed emotion regulation by measuring changes in self-reported emotion as participants regulate their responses to an actual emotional challenge (Feldner et al., 2006; Levitt et al., 2004). However, because this approach still relies on self-report of emotion, it is highly subject to demand characteristics and other sources of bias (Faith et al., 1998).

To overcome these limitations, the present study assessed emotion regulatory ability using a well-validated psychophysiological paradigm (Jackson et al., 2000; Lissek et al., 2008). In this paradigm, participants are alternately instructed to decrease, maintain, or increase their emotional reaction to distressing stimuli (e.g., negative pictures or threat of electric shock), and changes in emotional responding are measured using psychophysiological indices. Using this paradigm, multiple research groups have found that healthy individuals can regulate these indices during exposure to negative emotional stimuli (Jackson et al., 2000; Lissek et al., 2008).

This paradigm circumvents the methodological limitations of self-report described above. First, examination of emotion regulation in real time, during an actual emotional challenge, is not subject to recall bias. Second, it directly separates emotional reactivity (i.e., physiological response before participants receive regulation instructions) from voluntary emotion regulation (i.e., responses during decrease and increase trials). Third, the threat-of-shock variant of this task may be particularly relevant to panic disorder, as several studies have shown that individuals with panic disorder show abnormal startle responding during threat of unpredictable shock (Grillon et al., 2008; Shankman et al., 2013).
1.3.2  **Startle and Corrugator: Assessing Related but Distinct Affective Processes**

A fourth benefit of this paradigm is its use of validated physiological indices of emotion, which are not subject to demand characteristics and do not rely on participants’ imperfect estimation of their own abilities. The present study employed two psychophysiological indices—acoustic startle eye-blink reflex and *corrugator supercili* activity. The acoustic startle reflex is typically assessed by recording the peak contraction of the *orbicularis oculi* muscle in response to a sudden loud (> 80 dB) noise. It represents a fast (20-60 ms), involuntary response to potential danger and is closely related to the extended amygdala (Davis, 2006). The startle response is potentiated when danger is present or likely (Grillon, 2002). This potentiation is especially pronounced among individuals with panic disorder (Shankman et al., 2013) and other emotional disorders (Grillon et al., 2009), but can be dampened by agents such as alprazolam (Grillon et al., 2006). Based on these characteristics, startle potentiation to threat is thought to index defensive motivational states such as fear and anxiety (Davis, 2006).

The *corrugator supercili* muscle is important for facial expression of negative effect, including frowning and brow furrowing, and amenable to voluntary control (Miller et al., 2002). In contrast to the startle eye-blink reflex, corrugator shows tonic contraction during negative emotional states, spanning seconds or tens of seconds rather than tens of milliseconds. It is associated with responding to threat (e.g., Lang et al., 2011), but may also reflect complex emotions such as disappointment and regret (Wu and Clark, 2015), and is more sensitive than startle to disgust (Bradley et al., 2001), anger (Miller et al., 2002), and low positive emotion (Lang et al., 1993). Evidence therefore suggests that the startle reflex is sensitive to the underlying emotional state of fear or anxiety, whereas corrugator activity may be more sensitive to semi-voluntary facial expression of many negative emotional states.
Gross’s (1998; Gross & Jazaieri, 2014) process model posits both antecedent-focused (before or during emotion generation) and response-focused (after emotion generation) forms of emotion regulation. Insofar as startle indexes the emotional state of fear/anxiety, changes in startle potentiation during voluntary emotion regulation may index antecedent-focused regulation—i.e., individuals’ ability to change the experience of emotion itself. In contrast, changes in corrugator activity may be more sensitive to response-focused emotion regulation, which may include voluntary modulation of facial expression. Thus, assessing both the startle reflex and corrugator activity not only yields multiple measures of negative affect, but also allows examination of different emotion regulatory processes.

1.3.3 **Prior Studies**

Very few studies have examined instructed emotion regulation in panic disorder. In a study by Reinecke and colleagues (2015), participants received training in reappraisal strategies and were then instructed to alternately maintain or reappraise their emotional reactions to negative images. Individuals with panic disorder showed reduced HRV and increased prefrontal and limbic activity compared to healthy controls during maintain trials, but these differences were attenuated or eliminated during reappraisal trials. In another study (Levitt et al., 2004), individuals with panic disorder received a brief training in emotional acceptance or emotional suppression prior to a carbon dioxide inhalation challenge. Emotional acceptance training and self-reported use of acceptance during the challenge was associated with less self-reported anxiety and less avoidance, whereas self-reported use of suppression was associated with greater anxiety. In both of these studies, individuals received training in emotion regulation strategies prior to testing. Although this is clinically informative (e.g., regarding possible mechanisms of reappraisal- and mindfulness-based psychotherapies), it also likely obscures pre-existing group
or individual differences in emotion regulatory ability. To obtain a more valid measure of these individual differences, participants in the present study were not given specific instructions or training regarding how to regulate their emotional responding.

1.4  **Effortful Control as a Mechanism of Emotion Regulation**

Models from clinical, social, cognitive, and developmental psychology have long posited that mental processes are organized into an automatic, rapid, reactive, emotional system, and a controlled, deliberative, rational, non-emotional system (e.g., Gray and McNaughton, 2000; Kahneman, 2011; Metcalfe and Mischel, 1999; Rothbart and Rueda, 2005; see Carver et al., 2008; for a review). A key function of the latter (controlled, rational) system involves countermanding impulses or action tendencies generated by the former (automatic, reactive) system – an ability labeled *effortful control*. Effortful control is closely related to (and is arguably synonymous with) constructs including *cognitive control, executive control*, and *executive functioning*. Effortful control is important for inhibition of impulsive or habitual action (“inhibitory control”); planful activation of behavior despite impulses towards *inaction* (“activational control”); and shifting or maintaining focus of attention despite distractors (“attentional control”; Eisenberg et al., 2010; Evans and Rothbart, 2007). A dieter refusing a slice of cake, an agoraphobic individual attending a crowded concert, and a student looking up from her smartphone to attend to a lecture are all exercising effortful control.

Effortful control and related constructs are frequently discussed as mechanisms of emotion regulation (e.g., Joormann and Quinn, 2014; Lewis et al., 2010; Petersen and Posner, 2012), and functional connectivity studies have implicated the same networks in effortful control and emotion regulatory processes (e.g., Blair et al., 2007; Ochsner et al., 2012; Menon, 2011).
This research suggests close relationships between the within-individual, within-situation processes of effortful control and emotion regulation. However, few studies have examined the separate question of whether and how between-individual differences in effortful control and emotion regulatory abilities are related (Diaz and Eisenberg, 2015; see Joormann and Tanovic, 2015, for a review in the context of depression).

One possibility is that emotion regulatory dysfunction stems from a general deficit in effortful control capacity. That is, individuals with panic disorder may have difficulty regulating anxiety due to a more general deficit in their ability to effortfully control responding across emotional and non-emotional contexts. Consistent with this idea, performance on non-emotional effortful control tasks may be impaired in anxiety disorders (Pacheco-Unguetti et al., 2011, but see Heeren et al., 2015) and is associated with physiological indices of fear reactivity to threat of shock (Sarapas et al., 2016, unpublished data). Hendricks and Buchanan (2016) reported that effortful control abilities predicted changes in blink rate (a putative index of emotional suppression) and self-reported emotion, but not corrugator activity, during an emotion regulation task. The general deficit hypothesis has clinical relevance, as there is evidence that effortful control ability improves with training (Cohen et al., 2016; Hagger et al., 2010) and predicts response to treatment for internalizing disorders (Dunkin et al., 2000; Klumpp et al., 2014a; Langenecker et al., 2007a, 2008).

Emotion regulatory deficits may alternatively (or additionally) result from a specific disruption of capacity for effortful control in emotionally challenging contexts. Successful effortful control requires significant cognitive resources and is therefore easily disrupted by situational demands (Baumeister and Heatherton, 1996; Baumeister et al., 2007; Fishbach et al.,
2003; Metcalfe and Mischel, 1999; Mischel et al., 1989). Emotionally stressful situations are prime examples of situations that may deplete cognitive resources and impair effortful control (Blair et al., 2007; Gailliot et al., 2007; Melcher et al., 2011; Philippot and Brutoux, 2008). Consequently, individuals whose cognitive capacity is particularly disrupted by stressful situations may have especially poor emotion regulatory ability, even if they show normal effortful control in non-emotional contexts (Werner and Gross, 2010). Consistent with this specific disruption hypothesis, stress-related decrements in effortful cognitive abilities has been observed in generalized anxiety disorder (Vytal et al., 2016) and prospectively predict increases in depressive symptoms (Quinn and Joormann, 2015). However, no study to date has examined relationships between stressor-related effortful control and laboratory measures of emotion regulation.

1.5 **Aims and Hypotheses**

The present study had two broad aims. First, we assessed voluntary emotion regulatory ability in individuals with and without panic disorder using a validated psychophysiological paradigm. We did not make strong directional hypotheses, given that theoretical predictions and previous findings have variously suggested deficient, excessive, and paradoxical emotion regulation in panic disorder. However, based on somewhat more consistent evidence suggesting over-regulation of emotion in PD/A, we conducted secondary analyses comparing emotion regulation in PD/A versus PD/NA.

Our second aim was to examine relationships between emotion regulation and effortful control abilities in panic disorder. General effortful control capacity was assessed using two cognitive tasks yielding measures of set-shifting, inhibitory control, and attentional control. To
assess the degree to which effortful control capacity is disrupted under stress, participants completed alternate versions of these tasks during threat of unpredictable electric shock. We predicted that (1) emotional challenge would differentially disrupt effortful control capacity among individuals with panic disorder; (2) indices of effortful control would be positively correlated with emotion regulatory abilities; and (3) effortful control would statistically mediate group differences in emotion regulation.
2. METHOD

2.1 Participants

Seventy-five individuals were recruited from the community and local clinics, including 38 individuals with current panic disorder (15 with and 23 without agoraphobia) and 37 healthy controls. All participants provided written informed consent. Procedures were approved by the institutional review board at the University of Illinois at Chicago.

2.1.1 Enrollment Criteria

Inclusion criteria were age between 18 and 50, ability to read and write English, right-handedness (confirmed using Edinburgh Handedness Inventory – Revised, Williams, 2013; laterality quotient \( M = +89.7, SD = 17.3, \) range = +31.3 to +100.0), normal hearing in both ears, and normal or corrected-to-normal vision in both eyes. Exclusion criteria were personal or first-degree family history of manic or psychotic episode; personal history of attention-deficit/hyperactivity disorder or obsessive-compulsive disorder; current depressive disorder; current moderate or severe alcohol or substance use disorder; history of head injury with >15 min loss of consciousness or >30 min posttraumatic amnesia; head injury with any loss of consciousness in the past 3 months; history of electroconvulsive therapy; and neurological or medical illness known to affect cognition, symptoms or physiological responding (e.g., epilepsy, stroke, untreated hypothyroidism). The additional inclusion criterion for the panic disorder group was current panic disorder. The additional exclusion criterion for the control group was history of any mental disorder other than mild alcohol or substance use disorder. Participants were instructed not to use alcohol or recreational drugs within 12 hours of lab visits.
2.1.2 **Participant Flow**

Six hundred five participants completed an initial telephone eligibility screen. Of these, 93 (15.4%) appeared eligible and presented for the first study visit. Twelve of these individuals proved ineligible following more detailed diagnostic assessment. One participant withdrew and one participant was lost to follow-up between the first and second visit. One participant refused to complete the emotion regulation task, one participant’s data were unusable due to equipment failure, and two participants were excluded due to excessive artifact in both startle and corrugator data, resulting in the final sample of 75.

2.2 **Psychopathology Measures**

2.2.1 **Diagnostic Interviews**

Current and lifetime mental disorders were assessed using the Structured Clinical Interview for *DSM-5* (SCID-5; First et al., 2016). The SCID-5 was administered by the author and two other clinical psychology doctoral students. Interviewers were trained to criterion by watching the *SCID 101* training videos (Biometrics Research Department, 2002); observing interviews by raters previously trained to criterion, and completing two or three supervised interviews in which all diagnoses were in agreement with those made by the trained raters. First-degree family history of psychopathology was assessed using the Family History Screen (Weissman et al., 2000).

2.2.2 **Panic Disorder Severity**

All participants completed a battery of questionnaires including the Inventory for Depression and Anxiety Symptoms (IDAS, Watson et al., 2007; 2008), a well-validated self-report measure of internalizing psychopathology composed of broad and specific symptom
scales, as well as supplemental anxiety-related scales described by Watson and colleagues (2012). IDAS scales of interest for the present study included Panic (physiological symptoms associated with panic attacks), and Claustrophobia (fear and avoidance of crowds and small spaces), and Dysphoria (broad negative affect). Panic disorder participants also completed the 7-item clinician-administered Panic Disorder Severity Scale (PDSS; Shear et al., 1997).

2.3 **Procedure**

Procedures were divided into two lab visits. The first visit consisted of diagnostic interviewing and two effortful control tasks (one during threat of shock). The second visit consisted of the emotion regulation task and the remaining two effortful control tasks (one during threat of shock). To minimize effects of fatigue associated with effortful tasks (Hagger et al., 2010), participants completed less-effortful tasks (i.e., questionnaires or interviews) between effort-demanding tasks (i.e., emotion regulation or effortful control tasks) so that two effort-demanding tasks were never completed in immediate succession. Participants were also offered breaks following each task. Participants completed emotion regulation and effortful control tasks while seated in an electrically-shielded, sound-attenuated booth approximately 3.5-ft. from a 19-in computer monitor.

2.3.1 **Shock Work-Up**

Electric shocks were delivered during the emotion regulation task and two effortful control tasks. Electric shocks were 400 ms in duration and administered to the wrist of the participant's non-dominant (i.e., left) hand. To ensure equality in perceived shock aversiveness (Rollman and Harris, 1987), shock level was ideographically set to a level each participant found “highly annoying, but not painful.” The maximum possible shock level was 5 μA. Actual shock
values ranged from 0.2 μA to 5.0 μA ($M = 1.8$, $SD = 1.1$). Participants received a total of 9 shocks across all tasks.

2.3.2 **Emotion Regulation Task**

2.3.2.1 **Task Procedures**

Participants completed a previously-validated psychophysiological emotion regulation task (Figure 1; Jackson et al, 2000; Lissek et al., 2008). Stimuli for the task were presented using Psylab (Contact Precision Instruments, London, UK). The task consisted of threat trials, during which participants could receive an electric shock to the wrist at any time, and safe trials, during which participants received no shocks. During trials, participants viewed a slide reading either “SHOCK?” or “SAFE” to indicate the current trial type. Each trial lasted 12 s, with intertrial intervals (ITIs) lasting 8 s. Four seconds into each trial, instructions to increase, maintain, or decrease emotional response to the trial were presented through speakers (during safe trials, only instructions to maintain were presented). The task included 28 threat trials (9 suppress, 10 maintain, and 9 enhance) and 14 safe trials, and lasted 15 minutes (including a 45-second break at the midpoint). A shock was delivered during 5 of the 28 shock trials.

To simulate emotion regulation motivated by real-life consequences, participants were told that they would receive a $10 “bonus” if they both decreased and increased their emotional responding by at least 10% (Lissek et al., 2008). In reality, all participants received this “bonus,” and were debriefed accordingly at the end of the session. Participants were not instructed to use a

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1 Previous versions of the task employed instructions to “suppress,” “maintain,” or “enhance” emotion. The more common words “decrease” and “increase” were substituted for “suppress” and “enhance” to ensure comprehension by all participants (Davies, 2012).
specific emotion regulatory strategy during the task, but were told that they should not attempt to regulate by looking away from the screen or by generating a different emotion (Jackson et al., 2000; Lissek et al., 2008).

2.3.2.2 Dependent Measures

Electromyography (EMG) measures of corrugator activity and eye blink startle reflex to acoustic probes were recorded throughout the task. Startle probes were delivered 7-12 s after trial onset (i.e., 3-8 s after regulation instructions) during 7 trials of each condition, yielding measures of “regulated” responding for each condition. Seven safe trials and 7 threat trials (2 suppress, 3 maintain, 2 enhance) included a startle probe at 3 s (i.e., before regulation instructions) as a measure of “unregulated” response to threat and non-threat. A startle probe was never delivered within 7 s of another startle probe or within 10 s after a shock. Startle probes were 40-ms, 103-dB bursts of white noise with near-instantaneous rise time presented binaurally through headphones. To minimize effects of startle habituation during the emotion regulation task, participants completed two habituation phases including six startle probes prior to the regulation task (one habituation phase before and one after placement of shock electrodes).
EMG data were continuously recorded in Neuroscan 4.5 (Compumedics, Charlotte, NC) at a sampling rate of 2000 Hz using a bandpass filter of DC-500 Hz. Startle responses were recorded from two 4-mm silver-silver chloride electrodes placed over the *orbicularis oculi* muscle below the left eye (Fridlund and Cacioppo, 1986; Blumenthal et al., 2005). Corrugator activity was recorded from two electrodes placed over the *corrugator supercilii* muscle above the left eye (Fridlund and Cacioppo, 1986). A ground electrode was placed in the center of the forehead along the midline, and a noise-cancellation electrode was placed on the back of the neck along the midline.

2.3.3 **Effortful Control Tasks**

Participants completed two computerized behavioral tasks yielding three measures of effortful control ability: speeded set-shifting and inhibitory control from the Parametric Go/No-Go/Stop task (PGNGS, Langenecker, 2005; 2007b; Votruba and Langenecker, 2013), and attentional control from the Attention Network Test – Short Version (ANT-S, Fan et al., 2002). Both tasks were administered using E-Prime Professional 2.0 (Psychology Software Tools, Sharpsburg, PA).

To assess participant’s general capacity for effortful control as well as the degree to which effortful control is disrupted in emotionally challenging contexts, participants completed each task twice. During one of these administrations, participants were informed that they may receive between two and five shocks at any point during the task. Two shocks were actually delivered during each task, and trials immediately following these shocks were excluded from analyses. Shocks were triggered by E-Prime and delivered by Psylab. Task order was counterbalanced across participants such that (1) alternate versions of each task occurred during
separate lab visits and (2) participants completed one “safe” and one “threat” effortful control task during each visit.

2.3.3.1 **Parametric Go/No-Go/Stop Task**

The PGNGS is a modification of go/no-go and stop-signal tasks that yields measures of sustained attention, set-shifting, and inhibitory control. The latter two measures are of interest for the current study, as they are considered aspects of effortful control (Rothbart et al., 2005; 2006; Eisenberg et al., 2010). The PGNGS has demonstrated good retest reliability and convergent validity with other measures of executive control (Langenecker et al., 2007b).

The task consists of three conditions. During all conditions, letters are serially presented for 600 ms each. The first condition (“Go”) is a static RT task in which participants are instructed to respond as quickly as possible when one of three target letters appears, but withhold responding to all other letters. (Targets were ‘r,’ ‘s,’ and ‘t’ for one administration and ‘x,’ ‘y,’ and ‘z’ for the other administration.) During the second condition (“Go/No-Go”), the target value of letters shifts throughout the task. For example, if a participant responds to an ‘x,’ they should then respond only to a ‘y’ or ‘z,’ but *withhold* responding to another ‘x.’ If the participant next responds to a ‘z,’ they should then respond to an ‘x’ or ‘y,’ but withhold responding to another ‘z.’ During the third condition (“Go/Stop”), participants are instructed to respond to all three target letters. However, some targets are followed by a stop signal 250-400 ms after onset, requiring participants to inhibit responding. The Go condition includes 26 correct targets, the Go/No-Go condition includes 33 correct targets plus 12 lures, and the Go/Stop condition includes 28 correct targets plus 12 targets followed by stop signals. Each condition lasts 2 to 3 minutes.
Set-shifting scores were computed by subtracting average RT for correct responses during the Go/No-Go condition from average correct-response RT during the Go condition. Inhibitory control scores were computed by subtracting correct-response RT during the Go/Stop condition from correct-response RT during the Go condition.

2.3.3.2 Attention Network Test – Short Version

The ANT-S is a combination of cued RT (Posner, 1980) and Eriksen flanker (Eriksen and Eriksen, 1974) tasks and assesses efficiency of alerting, orienting, and attentional control. The attentional control measure is of primary interest for this study (Rothbart et al., 2005; 2006; Eisenberg et al., 2010). The ANT has demonstrated high retest reliability for attentional control (Fan et al., 2002).

During each trial, an arrow pointing right or left appears on-screen, flanked by arrows pointing in the same or opposite direction. Participants must indicate the direction of the center arrow, which sometimes requires resolving conflicting information (e.g., when a right-pointing arrow is flanked by left-pointing arrows). The array of arrows appears on either the top or bottom of the screen and is sometimes preceded by alerting or orienting cues. The task includes 144 trials, half with congruent flankers and half with incongruent flankers, and lasts approximately 10 minutes. Attentional control scores were computed by subtracting average correct-response RT for arrows with incongruent flankers from correct-response RT for arrows with congruent flankers.
2.4 **Physiological Data Processing**

Startle data were processed using Neuroscan. Data were first rectified and smoothed using a finite impulse response filter with a band pass of 28-40 Hz, then visually examined and scored for non-responses and missing blinks scored according to published guidelines (Blumenthal et al., 2005). Amplitude of the blink reflex was defined as the peak response within the 20-150 ms time frame following startle probe onset relative to pre-stimulus baseline. Values were positively skewed (average $z_{skew} = 4.87, p < .001$) and kurtotic (average $z_{kurtosis} = 2.60, p < .01$) and were therefore log transformed to normality ($z_{skew} = -0.84, ns, z_{kurtosis} = -0.90, ns$).

Analyses were conducted using blink amplitude (non-response trials excluded from condition averages), but results for blink magnitude (condition averages include values of for non-response trials) were similar.

Corrugator data were processed using BrainVision Analyzer 2.0 (Brain Products, Gilching, Germany). Data were divided into 1024 ms Hamming-windowed epochs overlapping by 50% and visually inspected for artifact (including blinks elicited by startle probes). Artifact-free data were subjected to a fast Fourier transform to derive estimates of spectral power density in the 45-200 Hz band for each condition. Values were positively skewed (average $z_{skew} = 9.92, p < .001$) and kurtotic (average $z_{kurtosis} = 16.86, p < .001$) and were therefore log transformed to normality ($z_{skew} = -0.52, ns, z_{kurtosis} = -0.23, ns$).

2.5 **Data Analysis**

2.5.1 **Missing Data**

Startle data for one participant were excluded due to excessive artifact. ANT-S data for one participants and PGNGS data for one participant were excluded due to extreme outliers (RTs
>3 SDs above the mean). Seven participants responded incorrectly to items embedded in questionnaires to check for random responding and were excluded from questionnaire analyses.

2.5.2 **Evaluation of Covariates**

We compared groups on demographic variables and examined whether dependent measures were associated with demographic, medication, or substance use variables. Variables found to be associated with dependent measures were included in analyses where appropriate.

2.5.3 **Task Effects**

To examine whether threat of shock effectively manipulated physiological responding during the emotion regulation task, we compared changes in startle magnitude and corrugator activity during the “unregulated” (i.e., pre-instruction) phase of threat versus safe trials using repeated measures analyses of variance (ANOVAs). To test for the predicted emotion regulatory effects, we used repeated measures ANOVAs to compare startle amplitude and corrugator activity following instructions to decrease, maintain, or increase emotional responding during the threat condition. We tested whether the ANT-S produced the predicted executive conflict effect using a repeated-measures ANOVA comparing RTs for stimuli with congruent versus incongruent flankers. Likewise, we used repeated-measures ANOVAs to test whether participants showed slower RTs during the PGNGS Go/No-Go and Go/Stop conditions compared to the Go condition.

2.5.4 **Emotion Regulation**

Group differences in emotion regulatory ability were examined using 2 (Condition: maintain\textsubscript{threat}, decrease\textsubscript{threat}) X 2 (Group: control, panic disorder) mixed design ANOVAs on
startle amplitude and corrugator activity. Secondary analyses examined differences between PD/A and PD/NA by substituting a 3-level Group (control, PD/NA, PD/A) factor. An additional secondary analysis tested for group differences in emotion enhancement by substituting a 2-level Instruction (maintain\textsubscript{threat}, increase\textsubscript{threat}) factor.

2.5.5 **Effortful Control**

To examine group differences in effortful control, as well as whether threatening contexts differentially disrupted effortful control among individuals with panic disorder, we conducted Condition (safe, threat) X Group mixed design ANOVAs on measures of effortful control from the PGNGS and ANT.

2.5.6 **Relationships of Emotion Regulation with Effortful Control**

Relationships between emotion regulatory ability (i.e., startle and corrugator emotion regulation scores) and effortful control (i.e., set-shifting, inhibitory control, and attentional control scores) were tested using Pearson correlations. For measures of effortful control found to be related to both panic disorder status and emotion regulation scores, path analyses were conducted in 5,000 bootstrap samples to test indirect effects of panic disorder status on emotion regulatory ability through the measure of effortful control (MacKinnon, 2008; Preacher and Hayes, 2008).
3. RESULTS

3.1 Participants

Demographic and clinical characteristics of the sample are presented in Table I. Groups did not differ in age, gender, racial/ethnic composition, or level of education. As expected, individuals with panic disorder reported more severe symptoms of panic, claustrophobia/agoraphobia, and general negative affect compared to controls, and had greater clinician-rated functional impairment and general symptom severity. These results were identical whether individuals with PD/A and PD/NA were analyzed as separate groups or combined into a single panic disorder group.

PD/A was associated with more severe self- and clinician-rated agoraphobia symptoms and more clinician-rated functional impairment than PD/NA. PD/A and PD/NA did not differ on self-reported panic or negative affect symptoms, but there were trends towards greater clinician-rated panic and general symptom severity in PD/A compared to PD/NA.

Comorbid lifetime diagnoses in the panic disorder group included agoraphobia (15 current, 1 past), specific phobia (16 current), social anxiety disorder (13 current), generalized anxiety disorder (15 current, 4 past), and other specified anxiety disorder (1 current); posttraumatic stress disorder (1 past) and other specified trauma- and stressor-related disorder (1 current); major depressive disorder (15 past); alcohol use disorder (2 current, both mild severity; 8 past, mild or moderate severity) and cannabis use disorder (4 current, mild severity; 1 past, moderate severity); binge eating disorder (2 past) and bulimia nervosa (1 past); excoriation disorder (1 current) and trichotillomania (1 past). One control participant had past history of mild alcohol use disorder, but controls were otherwise free of lifetime psychopathology. Twelve panic
## TABLE I
DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Panic without Agoraphobia</th>
<th>Panic with Agoraphobia</th>
<th>Group Differences</th>
<th>Pairwise Comparisons&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>28.0 (9.0)</td>
<td>28.8 (9.9)</td>
<td>28.3 (9.4)</td>
<td>( F &lt; 1, \text{ns} )</td>
<td>( \text{ns} )</td>
</tr>
<tr>
<td>Female</td>
<td>23 (62.2%)</td>
<td>17 (73.9%)</td>
<td>12 (80.0%)</td>
<td>( \chi^2(2) = 1.92, \text{ns} )</td>
<td>( \text{ns} )</td>
</tr>
<tr>
<td>Years of education</td>
<td>15.5 (2.2)</td>
<td>15.7 (1.7)</td>
<td>14.9 (2.1)</td>
<td>( F &lt; 1, \text{ns} )</td>
<td>( \text{ns} )</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>6 (16.2%)</td>
<td>4 (17.4%)</td>
<td>4 (26.7%)</td>
<td>( \chi^2(6) = 7.53, \text{ns} )</td>
<td>( \text{ns} )</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>6 (16.2%)</td>
<td>0 (0.0%)</td>
<td>3 (13.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>5 (13.5%)</td>
<td>3 (13.0%)</td>
<td>0 (0.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>18 (48.6%)</td>
<td>16 (69.6%)</td>
<td>9 (60.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple Races</td>
<td>2 (5.4%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td></td>
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</tr>
<tr>
<td><strong>Panic Symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDAS Panic</td>
<td>9.1 (2.5)</td>
<td>16.4 (6.5)</td>
<td>19.6 (8.0)</td>
<td>( F(2, 65) = 23.23, p &lt; .001 )</td>
<td>( \text{C &lt; PD/NA = PD/A} )</td>
</tr>
<tr>
<td>PDSS Total</td>
<td>-</td>
<td>10.7 (3.0)</td>
<td>13.1 (4.4)</td>
<td>( F(1, 36) = 3.87, p &lt; .10 )</td>
<td>( \text{PD/NA \leq PD/A} )</td>
</tr>
<tr>
<td><strong>Agoraphobia Symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDAS Claustrophobia</td>
<td>5.2 (0.9)</td>
<td>7.5 (3.9)</td>
<td>14.8 (6.4)</td>
<td>( F(2, 65) = 34.23, p &lt; .001 )</td>
<td>( \text{C &lt; PD/NA &lt; PD/A} )</td>
</tr>
<tr>
<td>PDSS Agoraphobia</td>
<td>-</td>
<td>1.2 (0.89)</td>
<td>2.4 (0.91)</td>
<td>( F(1, 36) = 16.36, p &lt; .001 )</td>
<td>( \text{PD/NA &lt; PD/A} )</td>
</tr>
<tr>
<td><strong>General Symptomatology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDAS Dysphoria</td>
<td>14.5 (5.8)</td>
<td>26.5 (7.4)</td>
<td>28.8 (9.9)</td>
<td>( F(2, 65) = 27.25, p &lt; .001 )</td>
<td>( \text{C &lt; PD/NA = PD/A} )</td>
</tr>
<tr>
<td>GAF Symptom Severity</td>
<td>81.7 (8.1)</td>
<td>56.0 (6.2)</td>
<td>51.9 (6.1)</td>
<td>( F(2, 72) = 134.50, p &lt; .001 )</td>
<td>( \text{C &gt; PD/NA = PD/A} )</td>
</tr>
<tr>
<td>GAF Impairment</td>
<td>84.0 (5.0)</td>
<td>65.2 (8.8)</td>
<td>55.2 (6.0)</td>
<td>( F(2, 72) = 121.25, p &lt; .001 )</td>
<td>( \text{C &gt; PD/NA &gt; PD/A} )</td>
</tr>
</tbody>
</table>

<sup>a</sup> \( \leq \) and \( \geq \) indicate differences significant at \( p < .10 \), whereas \( < \) and \( > \) indicate differences significant at \( p < .05 \).
disorder participants were taking psychiatric medications, including antidepressants \((n = 7)\) and anxiolytics \((n = 8)\).

3.2 **Evaluation of Potential Covariates**

Older participants showed greater slowing during the PGNGS Go/No-Go condition, \(r(72) = .46, p < .001\), and greater executive conflict during the ANT-S, \(r(72) = .31, p < .01\). Within the panic disorder group, individuals taking antidepressants showed less slowing during the PGNGS Go/Stop condition, \(t(36) = 3.53, p < .001\). No variable of interest was related to sex, race, or current use of anxiolytics, oral contraceptives, tobacco, or cannabis. Based on these results, age was included as a covariate in cross-sectional analyses of PGNGS and ANT-S data, and we conducted analyses of Go/Stop data both including and excluding individuals taking antidepressants.

3.3 **Basic Task Effects**

Participants exhibited greater startle amplitude, \(F(1, 73) = 30.61, p < .001, \eta^2_p = .30\), and corrugator activity, \(F(1, 74) = 7.69, p < .01, \eta^2_p = .09\), during pre-regulation threat periods than pre-regulation safe periods, indicating that threat of shock effectively manipulated physiological indices of defensive responding and negative affect. Emotion regulation instructions also affected startle amplitude, \(F(2, 144) = 19.22, p < .001, \eta^2_p = .21\), and corrugator activity, \(F(2, 148) = 14.96, p < .001, \eta^2_p = .17\). Follow-up analyses revealed a linear increase in responding from decrease\(_{\text{threat}}\) to maintain\(_{\text{threat}}\) to increase\(_{\text{threat}}\) for both startle, \(F(1, 72) = 29.56, p < .001\), and corrugator, \(F(1, 74) = 19.90, p < .001\). Emotion regulation scores (i.e., maintain\(_{\text{threat}}\) -
decrease threat) for startle and corrugator were not correlated, \( r(72) = .08, \text{ns} \), suggesting that these measures of emotion regulation were independent.

As expected, participants showed slower reaction times during the Go/Go-No-Go, \( F(1, 73) = 256.82, p < .001, \eta^2_p = .78 \), and Go/Stop, \( F(1, 73) = 572.44, p < .001, \eta^2_p = .89 \), conditions of the PGNGS task compared to the Go condition. Likewise, the ANT-S produced the predicted executive conflict effect, as participants responded more slowly to stimuli flanked by incongruent arrows than to those flanked by congruent arrows, \( F(1, 73) = 446.12, p < .001, \eta^2_p = .86 \). Set-shifting (i.e., \( RT_{\text{Go}} - RT_{\text{Go/No-Go}} \)) and inhibitory control (i.e., \( RT_{\text{Go}} - RT_{\text{Go/Stop}} \)) scores were positively correlated, \( r(72) = .30, p < .01 \). However, attentional control scores (i.e., \( RT_{\text{congruent}} - RT_{\text{incongruent}} \)) were not significantly correlated with set-shifting, \( r(71) = .19, \text{ns} \), or inhibitory control, \( r(71) = -.17, \text{ns} \).

3.4 Emotion Regulation Task

Condition (maintain, decrease) X Group (control, panic disorder) ANOVAs revealed lower startle amplitude and corrugator activity following instructions to decrease compared to maintain, consistent with the task effects just described. These analyses did not indicate main effects of Group or Condition X Group interactions (all \( Fs < 1 \)).

When individuals with panic disorder were divided into subgroups with or without agoraphobia, similar main effects again emerged for Condition. However, these analyses also revealed Condition X Group interactions for startle amplitude, \( F(2, 71) = 3.38, p < .05, \eta^2_p = .09 \), and corrugator, \( F(2, 72) = 4.03, p < .05, \eta^2_p = .10 \) (Figure 2). Individuals with PD/A showed greater startle suppression, \( t(71) = 2.60, p < .05 \), and corrugator suppression, \( t(72) = 2.72, p < \).
.01, than individuals with PD/NA. The PD/A group also showed greater corrugator, $t(72) = 2.40$, $p < .05$, and (at trend) startle suppression, $t(71) = 1.76$, $p < .10$, compared to controls. Although startle and corrugator suppression were numerically lower in PD/NA compared to controls, these differences were non-significant ($ps > .20$). All pairwise contrasts remained significant following correction for familywise error, with the exception of the trend-level difference between PD/A and controls for startle suppression, which dropped to non-significance. Differences between PD/A and PD/NA remained significant after adjusting for clinician-rated (PDSS Total) or self-rated (IDAS Panic) panic disorder symptom severity, suggesting that these results are not due to group differences in symptom severity.
Individuals with panic disorder did not differ from controls in their ability to increase startle or corrugator responding when instructed to do so. This result did not change when participants with and without agoraphobia were examined separately.

### 3.5 Effortful Control Tasks

Condition (safe, threat) X Group (control, PD/NA, PD/A) ANCOVAs adjusted for age did not reveal main effects of Condition or Condition X Group interactions for any of the three effortful control variables (all $F$s < 1), indicating that threat of shock did not affect task performance for any group. These analyses did show a main effect of Group on attentional control, $F(2, 69) = 3.14, p < .05, \eta^2_p = .08$ (Figure 3). Individuals with PD/NA showed poorer attentional control compared to PD/A, $t(69) = 2.31, p < .05$, and healthy controls, $t(69) = 2.07, p < .05$, who did not differ from one another ($t < 1$). The difference between PD/NA and PD/A remained significant after adjusting for clinician-rated (PDSS Total) or self-rated (IDAS Panic) panic disorder symptom severity. There were no effects of Group for set-shifting or inhibitory control ($F$s < 1). Results for inhibitory control did not differ when individuals taking antidepressants were excluded from analysis.

Because the threat condition failed to affect task performance, effortful control scores from the safe condition of each task were used in the following analyses. Substituting scores based on average performance across the safe and threat conditions yielded a very similar, but slightly weaker, pattern of results.
3.6 **Relationships of Emotion Regulation with Effortful Control**

As shown in Table II, startle suppression ability was positively associated with set-shifting, inhibitory control, and attentional control. An effortful control composite consisting of the mean standardized value across these three measures explained 25% of the variance in startle suppression ability (Figure 4). In contrast, corrugator suppression trended towards a negative association with set-shifting but was otherwise unrelated to effortful control measures. Results for inhibitory control did not differ when individuals taking antidepressants were excluded from analysis.
Because panic disorder status, attentional control, and emotion regulatory ability were interrelated, we examined whether PD/NA and/or PD/A status had indirect effects on emotion regulation due to attentional control. Path analyses in 5,000 bootstrap samples revealed that (non-significantly) lower levels of startle suppression in non-agoraphobic panic disorder were statistically mediated by poor safe-condition attentional control, $\beta = -.11, 95\% \text{ CI } [-.34, -.01]$. Indirect effects of agoraphobic panic disorder on startle suppression were not significant, $\beta = .01, 95\% \text{ CI } [-.10, .19]$. 

**TABLE II**

PEARSON CORRELATIONS AMONG MEASURES OF EMOTION REGULATION AND EFFORTFUL CONTROL

<table>
<thead>
<tr>
<th>EC Measure</th>
<th>Emotion Regulation Measure</th>
<th>Startle</th>
<th>Corrugator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attentional Control</td>
<td>.25*</td>
<td>.05</td>
<td></td>
</tr>
<tr>
<td>Set-Shifting</td>
<td>.27*</td>
<td>-.20*</td>
<td></td>
</tr>
<tr>
<td>Inhibitory Control</td>
<td>.40***</td>
<td>-.14</td>
<td></td>
</tr>
<tr>
<td>EC Composite</td>
<td>.50***</td>
<td>-.14</td>
<td></td>
</tr>
</tbody>
</table>

$+ p < .10, * p < .05, *** p < .001$
Figure 4. Relationship between effortful control ability and voluntary emotion regulatory ability. Effortful control composite scores represent mean standardized inhibitory control, set-shifting, and attentional control scores from Parametric Go/No-Go/Stop Task and Attention Network Test – Short Version. Higher values indicate more efficient effortful control. Startle suppression scores represent change scores for log-transformed startle amplitude during instructions to decrease versus maintain emotional responding to unpredictable threat of shock. Lower values indicate greater “emotion regulation.”
4. DISCUSSION

Emotion regulation is a key variable for understanding how emotional and cognitive processes interact to confer risk for anxiety disorders. In contrast to previous research, which has largely relied on self-report, the present study examined changes in two physiological indices of emotion as participants attempted to regulate their emotional responding to an actual threat. Although individuals with panic disorder did not differ from controls in initial analyses, subsequent analyses revealed that panic disorder with agoraphobia was associated with greater emotion regulatory ability compared to panic disorder without agoraphobia or healthy controls. This pattern of results held for both startle- and corrugator-based measures of emotion regulation and was not accounted for by differences in symptom severity. Participants’ ability to regulate startle responding was positively associated with all three indices of effortful control assessed (i.e., attentional control, set-shifting, and inhibitory control), which together explained 25% of the variance in startle suppression. Finally, individuals with PD/NA demonstrated deficits in attentional control, and these deficits statistically accounted for impaired emotion regulation in this group.

4.1 Emotion Regulation in Panic Disorder: The Role of Agoraphobia

The present results may elucidate previous studies showing divergent patterns of physiological threat reactivity in panic disorder with versus without agoraphobia. Although panic disorder is generally associated with heightened startle responding to threat (Grillon et al., 2008; Shankman et al., 2013), PD/A has been associated with reduced startle reactivity in several studies (Cuthbert et al., 2003; McTeague et al., 2011; McTeague and Lang, 2012). This blunted reactivity has previously been attributed to factors such as reduced autonomic flexibility (Cuthbert et al., 2003) or deleterious effects of chronic stress on the defensive system (McTeague
and Lang, 2012). The present results suggest that these diminutions in physiological responding may also reflect active down-regulation of responding, not merely a passive lack of reactivity. This possibility is supported by findings of increased activation in prefrontal regions during threat processing among individuals with more severe agoraphobia and panic symptoms (Reinecke et al., 2015).

The present findings are most consistent with models that conceptualize agoraphobia as maladaptive over-regulation of negative emotion in the form of chronic avoidance (Bouton et al., 2001; Craske and Barlow, 2008). In further support of this idea, evidence suggests that anxious avoidance is associated with diminished startle reactivity. In a behavioral avoidance paradigm employed by Hamm and colleagues (2016), individuals with panic disorder with agoraphobia were asked to remain in a small, dark, locked chamber for as long as possible, but given the option to terminate the exposure prior to the maximum duration (10 minutes, unknown to participants). Participants who engaged in avoidance by ending the exposure early showed diminished startle responding (but heightened skin conductance and heart rate) prior to doing so. Similarly, Löw and colleagues (2015) reported lower startle responding to threat when opportunities for avoidance were present versus absent. Although participants in the present study were not afforded opportunities for behavioral avoidance, these findings suggest that individuals with PD/A may have been adept at using cognitive or other covert forms of avoidance to suppress emotional responding. Likewise, avoidance or other regulatory strategies may explain findings of blunted startle reactivity in posttraumatic stress disorder (Katz et al., in press) and other anxiety populations (McTeague and Lang, 2012).
4.2 **Emotion Regulation and Effortful Control**

Dual-process theories (Carver et al., 2008) and functional connectivity studies (Blair et al., 2007; Dosenbach et al., 2006; Ochsner et al., 2012; Kelley et al., 2015; Menon, 2011) have increasingly implicated effortful control in a suite of self-regulatory abilities, including emotion regulation. Neural regions important for effortful control of behavior, including anterior cingulate cortex, dorsolateral prefrontal cortex, and other prefrontal areas, show extensive structural and resting functional connectivity with the extended amygdala nuclei that subserve fear and anxiety (Bracht et al., 2009; Torrissi et al., 2015). Functional connectivity between anterior cortical regions and the amygdala is further increased during emotion regulation (e.g., Blair et al., 2007) and predicts response to psychotherapy for anxiety disorders (Klumpp et al., 2014b). These findings provide evidence that similar within-person processes underlie effortful control and emotion regulation. However, the fact that effortful control and emotion regulation are associated with similar or overlapping neural circuitry does not necessarily imply that *individual differences* in these two abilities are related (Cervone, 2005; Diaz and Eisenberg, 2015; Sarapas et al., 2014).

Few studies have examined relationships among individual differences in effortful control and emotion regulatory ability (see Joormann and Tanovic, 2015, for a review in the context of depression). Pe and colleagues (2013) reported that ability to update emotional information in working memory was related to trait and momentary ratings of reappraisal effectiveness. However, in addition to relying on self-report measures of emotion regulatory ability, this study did not assess relationships between emotion regulation and *non*-emotional effortful control. This would provide a stronger test of whether individual differences in emotion regulation are related to broader effortful control abilities. In an undergraduate sample,
Hendricks and Buchanan (2016) found that performance on response inhibition and working memory updating tasks predicted reductions in blink rate and self-reported negative affect, but not corrugator activity, during attempts to suppress or reappraise negative emotion.

The present results replicate and extend these findings in several ways. First, we replicated the finding that corrugator suppression is largely unrelated to effortful control, but showed that reductions in the startle reflex, a well-validated measure of defensive responding, were related to all measures of effortful control assessed. Second, individuals with PD/NA demonstrated deficits in attentional control, which statistically accounted for emotion regulatory deficits in this group. This finding emerged despite a lack of significant differences between PD/NA and controls on emotion regulation, which may reflect low statistical power or the presence of a competing, unmeasured mediator with opposite effects (Hayes, 2009). Conversely, although individuals with agoraphobia did differ from controls and PD/NA on emotion regulation, these differences were not accounted for by attentional control. Deficits in emotion regulation in PD/NA may therefore reflect broader difficulties with attentional or cognitive control, whereas enhanced emotion suppression in PD/A likely reflects other mechanisms, such as a higher propensity for cognitive avoidance or lower distress tolerance.

Contrary to hypotheses, effortful control abilities were not affected by threatening contexts for either controls or panic participants. Although some research has reported effects of threat contexts on cognitive performance, these effects are moderated by many factors including clinical variables (Vytal et al., 2016), temperament (Grillon et al., 2016), task difficulty (Patel et al., 2016; Vytal et al., 2016), and response modality (Patel et al., 2016). Several previous studies have also reported null findings for this effect (e.g., Balderson et al., in press; Quinn and
Joormann, 2015). The present findings are most consistent with effects of a dispositional or general deficit in effortful control on emotion regulatory ability; however, the possibility that threat contexts further disrupt effortful control and emotion regulatory abilities in some circumstances cannot be ruled out.

4.3 **Divergence and Convergence Across Multiple Measures**

Startle responding is a non-voluntary, subcortically-mediated reflex sensitive to defensive motivational states such as fear and anxiety (Davis, 2006). In contrast, *corrugator supercilii* activity reflects semi-voluntary facial expression of emotion (Miller et al., 2002) and is linked to negative valence more broadly. Consistent with their discriminant validity, startle suppression and corrugator suppression were uncorrelated in the present sample and differentially related to effortful control. In this context, the similar group differences in emotion regulatory ability observed for both startle and corrugator supports the robustness of the present findings. In the framework of Gross’s process model (1998; Gross & Jazaieri, 2014), these findings suggest that agoraphobic participants were adept at modulating not only semi-voluntary facial expression of emotion, but also the less-voluntary defensive emotional states that give rise to the startle reflex (i.e., fear and anxiety). That effortful control abilities were related to suppression of startle, but not corrugator, may indicate that regulation of fear and anxiety requires greater effortful control than modulation of facial expression. This is consistent with Gross’s model, which posits “cognitive change” as a key process for antecedent-focused, but not response-focused, emotion regulation.

Measures of effortful control were also not consistently interrelated. This is in line with theoretical and empirical literature indicating that measures of different executive functions are
often uncorrelated and that “executive functioning” may not be a unitary entity (Jurado and Roselli, 2007; Salthouse et al., 2003). Effortful control is also posited to be a multidimensional construct consisting of attentional control, inhibitory control, and activational control (Eisenberg et al., 2010; Evans and Rothbart, 2007). Again, the fact that all three measures of effortful control were associated with startle suppression despite their inconsistent correlations with one another speaks to the robustness of these findings.

4.4 Implications for Treatment

PD/A is more persistent (Nay et al., 2013) and less responsive to treatment (Porter and Chambless, 2015; Schat et al., 2013) than PD/NA. Indeed, in a systematic review, Porter and Chambless (2015) report that agoraphobic avoidance is the most consistent predictor of poor response to cognitive-behavioral therapy for panic disorder (whereas panic disorder severity generally does not predict outcome). A potential explanation for poor clinical outcomes in PD/A suggested by the present results is that these individuals may suppress emotional and physiological responding during exposures, such that they less frequently experience levels of fear activation sufficient for habituation or extinction. Indeed, Craske and colleagues (2014) argue that premature reductions in fear may act as safety signals that prevent inhibitory learning, particularly for individuals with the “fear of fear” characteristic of panic disorder. Agoraphobic individuals may therefore benefit from more tailored interventions designed to prevent covert emotional suppression during interoceptive and in vivo exposures. Liebscher and colleagues (2016) recently reported that patients showed greater reductions in agoraphobic symptoms following therapist-guided rather than self-guided exposures, supporting the need for greater treatment tailoring for this symptom dimension.
In contrast, the fact that attentional control ability statistically accounted for emotion regulatory deficits in PD/NA could suggest attentional control or other aspects of effortful control as targets for treatment. Indeed, a recent report indicates that effortful control training reduces amygdala reactivity and behavioral interference due to aversive stimuli (Cohen et al., 2016). However, despite evidence of atemporal mediation, individuals with PD/NA did not differ significantly from controls in emotion regulatory ability. Moreover, the above discussion of excessive emotion regulation in PD/A indicates that increased capacity to effortfully control emotion is not necessarily an unalloyed good (Bouton et al., 2001; Craske et al., 2014). Further investigation of the correlates of impaired effortful control in PD/NA is needed to assess whether this represents an appropriate treatment target.

4.5 Strengths and Limitations

Several limitations should be considered in interpreting this study. First, cell ns for analyses comparing agoraphobic and non-agoraphobic panic disorder were small, and the present results warrant replication in a larger sample. Nonetheless, the fact that similar emotion regulatory effects were observed for both startle and corrugator, despite the lack of correlation between these measures, supports the robustness of the results reported here. Second, although we demonstrated atemporal mediation of group differences in emotion regulation via attentional control, the study’s cross-sectional design precludes any inferences about causation (Winer et al., in press). Interpretation of this finding is further limited by the lack of a direct relationship between PD/NA and emotion regulatory ability. Third, the requirement that all participants have current panic disorder increased internal validity, but limits generalizability to other anxiety or internalizing disorders. This is particularly true given the divergent findings for panic disorder with versus without agoraphobia. Future studies may employ a more “RDoC-ian” approach by
examining emotion regulation and effortful control among participants with a broad range of emotional disorders, or by recruiting participants based on level of anxious arousal, anxious avoidance, or emotion regulatory ability.

The study also benefitted from several strengths. The collection of physiological and behavioral measures during an actual emotional challenge avoided limitations inherent in the retrospective self-report measures employed by many previous studies. Replication of several findings across multiple indices of emotion regulatory ability and effortful control provided evidence for the robustness of the present results. Finally, the study employed a well-characterized clinical sample, which increases the clinical relevance of findings. Exclusion of individuals with current depression or moderate to severe current substance use disorders also allows several alternative explanations for the present results to be ruled out.

4.6 Conclusion

This study examined differences in voluntary emotion regulation associated with panic disorder as well as cognitive mechanisms that might account for these differences. Findings indicated an enhanced ability to suppress negative emotion in panic disorder with agoraphobia. Better performance on behavioral measures of effortful control predicted greater ability to suppress defensive responding, and performance on one effortful control measure statistically accounted for emotion regulatory deficits in non-agoraphobic panic disorder. These results buttress a growing literature on relationships between effortful control and emotion regulation, and support unique etiological and maintenance factors for panic disorder with versus without agoraphobia. Panic with agoraphobia may be maintained by maladaptive over-regulation of anxiety (Bouton et al., 2001; Craske and Barlow, 2008), whereas panic without agoraphobia may
result in part from a reduced ability to effortfully modulate attention (Friedman and Thayer, 1998). Findings may point towards more targeted and efficacious treatments for both varieties of panic disorder.


Balderston NL, Vytal KE, O'Connell K, Torrisi S, Letkiewicz A, Ernst M, Grillon C. Anxiety patients show reduced working memory related DLPFC activation during safety and threat. *Depress Anxiety.* In press.


Davis, M. Neural systems involved in fear and anxiety measured with fear-potentiated startle. 

Diaz A, Eisenberg N. The process of emotion regulation is different from individual differences in emotion regulation: conceptual arguments and a focus on individual differences. 


Torrisi S, O’Connell K, Davis A, Reynolds R, Balderston N, Fudge JL, Grillon C, Ernst M. Resting state connectivity of the bed nucleus of the stria terminalis at ultra-high field. 

*Hum Brain Mapp.* 2015;36:4076-88.

Townsend J, Altshuler LL. Emotion processing and regulation in bipolar disorder: a review. 


Tull MT, Rodman SA, Roemer L. An examination of the fear of bodily sensations and body hypervigilance as predictors of emotion regulation difficulties among individuals with a recent history of uncued panic attacks. *J Anxiety Disord.* 2008;22:750-60.


Williams SM. A major revision of the Edinburgh Handedness Inventory. *ResearchGate*, 2013.
https://www.researchgate.net/publication/257352463_A_major_revision_of_the_Edinburgh_Handedness_Inventory.


APPENDIX

UNIVERSITY OF ILLINOIS
AT CHICAGO

Office for the Protection of Research Subjects (OPRS)
Office of the Vice Chancellor for Research (MC 672)
203 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227

Approval Notice
Initial Review (Response To Modifications)

May 17, 2013

Casey Sarapas
Psychology
Psychology
1007 W. Harrison Street, M/C 285
Chicago, IL 60607
Phone: (781) 572-6186

RE: Protocol # 2013-0182
“Emotion Regulation and Physiology”

Dear Mr. Sarapas:

Your Initial Review (Response To Modifications) was reviewed and approved by the Expedited review process on May 9, 2013. You may now begin your research.

Please note the following information about your approved research protocol:

Protocol Approval Period: May 9, 2013 - May 9, 2014
Approved Subject Enrollment #: 140
Additional Determinations for Research Involving Minors: These determinations have not been made for this study since it has not been approved for enrollment of minors.

Performance Sites: UIC
Sponsor: National Institute of Mental Health
PAF#: 2013-00471
Grant/Contract No: F31 MH100823
Grant/Contract Title: Patterns and Mediators of Emotion Regulatory Disturbance in Panic Disorder

Research Protocol:
   a) Emotion Regulation and Physiology, PI: Casey Sarapas, M.A., Version 3, 05/02/2013

Recruitment Materials:
   a) Flyer "Do you experience panic attacks", Version 2, 04/09/2013
Informed Consents:

a) Subject Information Sheet, Version #1, 04/09/2013
b) Participant Debriefing Sheet, Version 1, 04/09/2013
c) Emotion Regulation and Physiology - C, Version 3, 05/02/2013
d) Emotion Regulation and Physiology - P, Version 3, 05/02/2013
e) Alteration of informed consent granted for verbal consent to conduct phone screening (using the Subject Information Sheet) under 45 CFR 46.116(d)
f) Alteration of informed consent granted for deception (compensation for experimental session, use of the Participant Debriefing Sheet) under 45 CFR 46.116(d)
g) Waiver of Signed Consent Document granted for verbal consent to conduct phone screening (using the Subject Information Sheet), under 45 CFR 46.117

Please note the Review History of this submission:

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<tr>
<th>Receipt Date</th>
<th>Submission Type</th>
<th>Review Process</th>
<th>Review Date</th>
<th>Review Action</th>
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<td>Response To Modifications</td>
<td>Expedited</td>
<td>05/09/2013</td>
<td>Approved</td>
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</tbody>
</table>

Please remember to:

⇒ Use your research protocol number (2013-0182) on any documents or correspondence with the IRB concerning your research protocol.

⇒ Review and comply with all requirements on the enclosure, "UIC Investigator Responsibilities, Protection of Human Research Subjects" (http://tijger.uic.edu/depts/ovcr/research/protocolreview/irb/policies/0924.pdf)

Please note that the UIC IRB has the right to seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact OPRS at (312) 996-1711 or me at (312) 413-3788. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.
Sincerely,

Rachel Olech, B.A., CIP
Assistant Director, IRB # 3
Office for the Protection of Research Subjects

Enclosures:

1. **Informed Consent Documents:**
   a) Subject Information Sheet, Version #1, 04/09/2013
   b) Participant Debriefing Sheet, Version 1, 04/09/2013
   c) Emotion Regulation and Physiology - C, Version 3, 05/02/2013
   d) Emotion Regulation and Physiology - P, Version 3, 05/02/2013

2. **Recruiting Materials:**
   a) Flyer "Do you experience panic attacks", Version 2, 04/09/2013
   b) Flyer "Research Volunteers Needed", Version 2, 04/09/2013
   c) Ads to be posted on craigslist.org and UIC Massmail, Version #1, 04/09/2013

cc: Joe L. Martinez, Psychology, M/C 285
    Stewart Shankman, Faculty Sponsor, Psychology, M/C 285
    OVCRR Administration, M/C 672
VITA

NAME: Casey Sarapas

EDUCATION: Ph.D., Clinical Psychology, University of Illinois at Chicago, Chicago, Illinois, 2016

M.A., Clinical Psychology, University of Illinois at Chicago, Chicago, Illinois, 2011

B.S., Psychology, Fordham University, Bronx, New York, 2007

CLINICAL EXPERIENCE:

VA Maryland Health Care System / University of Maryland School of Medicine Psychology Internship Consortium, Baltimore, Maryland: Neuropsychology Track, 2015-2016


Neuropsychology Service, University of Illinois Hospital and Health Sciences System, Chicago, Illinois: Adult Neuropsychology Practicum, 2012-2013

Office of Applied Psychological Services, University of Illinois at Chicago, Chicago, IL: Practicum in Psychological Assessment, 2010-2011

Office of Applied Psychological Services, University of Illinois at Chicago, Chicago, IL: Practicum in Psychotherapy, 2010-2014

GRANTS AND FELLOWSHIPS:

Ruth L. Kirschstein National Research Service Award, National Institute of Mental Health: F31 MH100823 “Patterns and Mediators of Emotion Regulatory Disturbance in Panic Disorder,” 2013-2016

Predoctoral training appointment, National Institute of Mental Health: T32 MH067631 “Training in the Neuroscience of Mental Health,” 2012-2013

Chancellor’s Graduate Research Fellowship, University of Illinois at Chicago: “Genetic Bases of Internalizing Disorders: Examination of Two Physiological Mediators,” 2012-2013

HONORS AND AWARDS:

Outstanding Intern Award, VA Maryland / University of Maryland Internship Consortium, Baltimore, Maryland, 2016

Award for Excellence in Clinical Psychology, Department of Psychology, University of Illinois at Chicago, Chicago, Illinois, 2015
Student Poster Award, Society for a Science of Clinical Psychology, 2013

Honorable Mention, Smadar Levin Award, Society for Research in Psychopathology, 2011

PROFESSIONAL MEMBERSHIPS:
- American Academy of Clinical Neuropsychology
- Association for Psychological Science
- International Neuropsychological Society
- Society for Clinical Neuropsychology (APA Div. 40)
- Society for Research in Psychopathology
- Society for a Science of Clinical Psychology (APA Div. 12, Sec. III)

PEER-REVIEWED PUBLICATIONS:


Sarapas C, Katz AC, Nelson BD, Campbell ML, Bishop JR, Robison-Andrew EJ, Altman SE, Gorka SM, Shankman SA. Are individual differences in appetitive and defensive motivation related? A


BOOK CHAPTERS AND OTHER PUBLICATIONS:


Sarapas C, Blok D, Moricelli AS, Rosales G, Shankman SA. From cold to hot cognition: Linking basic attentional abilities and biased attention to threat. Poster presented at: 26th Annual Meeting of the Society for Research in Psychopathology; October, 2012; Ann Arbor, MI.

