Does Functional Variation in Cognitive Control Systems of the Brain Link Reappraisal to the Metabolic Syndrome

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DOES FUNCTIONAL VARIATION IN COGNITIVE CONTROL SYSTEMS OF THE BRAIN LINK REAPPRAISAL TO THE METABOLIC SYNDROME

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Negative emotionality is associated with an increased risk for developing the metabolic syndrome (MetS). Presumably, negative emotionality partly confers such risk via alterations in peripheral autonomic and neuroendocrine effector pathways that promote metabolic pathophysiology. Conversely, protection against risk for the MetS may be conferred by an individual's tendency to use cognitive strategies to regulate negative emotions. However, the brain systems by which cognitive emotion regulation relates to the MetS are unknown. Accordingly, we examined whether prefrontal and cingulate brain systems that jointly support cognitive emotion regulation and control peripheral physiological responses to negative emotional states represent a pathway linking emotion regulation to the MetS. Middle-aged adults (N=139; 74 men; mean age, 40.39 ± 6.2 years) underwent an fMRI scan while performing a Stroop color-word task that requires cognitive control, evokes a negative emotional state, and engages prefrontal and cingulate brain areas. Individual differences in self-reported tendencies to use cognitive reappraisal as an emotion regulation strategy were assessed by the Emotion Regulation Questionnaire (ERQ). The presence of the MetS was determined using the criteria of the National Cholesterol Education Program, Adult Treatment Panel III. After adjusting for age and sex, frequent cognitive reappraisal usage was associated with reduced likelihood of having

the MetS and with meeting fewer MetS criteria. Moreover, fMRI psychophysiological interaction analyses revealed that increasing task-evoked functional connectivity between the dorsal anterior cingulate (dACC) and dorsolateral prefrontal cortex (DLPFC) was associated with frequent cognitive reappraisal usage, reduced presence of the MetS, and meeting less MetS criteria, net the influence of age and sex. In an exploratory mediation analysis, this positive dACC-DLPFC connectivity mediated the association between cognitive reappraisal and the MetS. Individuals who frequently use cognitive reappraisal may be at lesser MetS risk in part via an enhanced capacity to recruit prefrontal cognitive control systems during negative affective states.

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1.0 INTRODUCTION

1.1 EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF THE METABOLIC SYNDROME

The metabolic syndrome (MetS) refers to a premorbid clustering of cardiometabolic risk factors within an individual. These risk factors include central obesity, glucose intolerance, atherogenic dyslipidemia, hypertriglyceridemia, and elevated blood pressure. The MetS is clinically important because it confers risk for type II diabetes, endpoints of cerebrovascular disease (e.g., hemorrhagic and ischemic strokes), atherosclerotic coronary heart disease (CHD), and premature cardiovascular mortality among otherwise healthy individuals – above-and-beyond the risk conferred by its individual components alone (Bataille et al., 2006; Boden-Albala et al., 2008; Galassi, Reynolds, & He, 2006; Gami et al., 2007; Lakka et al., 2002; Li et al., 2008; Sattar et al., 2003). Further, the MetS and its components are becoming increasingly prevalent, with recent epidemiological estimates indicating that about one-third of the U.S. adult population meets formal criteria for having the MetS (Ervin, 2009; Ford, Giles, & Dietz, 2002). This increasing prevalence has been associated with a commensurate rise in the prevalence of obesity, type II diabetes, and insulin resistance (a precursor to type II diabetes; Zimmet, Alberti, & Shaw, 2001).

Yet despite epidemiological associations between the MetS, obesity, type II diabetes, and insulin resistance, it is important to note that these conditions do not have a one-to-one

relationship with each another (Mendez, Goldberg, & McCabe, 2010). For instance, obese and overweight individuals do not always present with insulin resistance, and normal weight individuals can exhibit insulin resistance (Abbasi, Brown, Lamendola, McLaughlin, & Reaven, 2002; Ruderman, Chisholm, Pi-Sunyer, & Schneider, 1998). Moreover, the presence of the MetS does not necessarily correspond to an insulin resistant state for a given individual (Cheal et al., 2004; Liao et al., 2004; Salazar et al., 2011; Sierra-Johnson et al., 2006). Such complex interrelationships underscore the importance of considering the MetS as a multifaceted and complex pathophysiological condition (Mendez et al., 2010). In addition, it is important to appreciate existing evidence that the *clustering* (or aggregation) of the metabolic and cardiovascular risk factors that comprise the MetS occurs more often than by chance alone (Alberti et al., 2009). Such nonrandom clustering raises the possibility that common or shared pathogenic mechanisms or processes may relate to the development of the MetS or elevate risk for MetS component clustering (e.g., Muldoon et al., 2006; Williams et al., 2010). Hence, there is a need to further delineate the complex and potentially common pathophysiological processes that influence MetS risk and, consequently, unfavorable endpoints of its related chronic diseases.

It is important to note here, however, that efforts to characterize MetS risk factors and their correlates are further complicated by the lack of evidence-based guidelines for treating individuals meeting MetS criteria. As noted above, this complication stems in part from the fact that no specific or single pathophysiological process (or set of processes) has been identified to account for the clustering of syndrome components. For that reason, MetS prevention and treatment efforts are based largely on pharmacological approaches to affect individual MetS components, which introduces the possibility of adverse drug-drug interactions and related adverse events that are preferably avoidable. Such approaches also introduce concerns over

adherence, given the complicated drug regimens engendered by treating multiple cardiovascular disease risk factors through polypharmacy. By contrast, behavioral and lifestyle interventions, such as programs to change physical activity levels and dietary habits, may be more preferable than pharmacological approaches –insofar as such interventions may help reduce the prevalence and incidence (i.e., new cases) of the MetS at the population level without the costs and consequences typically associated with pharmacological approaches (Mendez et al., 2010). However, attempts to employ behavioral and lifestyle interventions can prove to be problematic because of their time-consuming nature and because of the demands they place on individuals for achieving long-term compliance (Butryn, Webb, & Wadden, 2011).

In view of the above, there remains a need to improve the efficacy of existing MetS risk prediction, stratification, prevention, and intervention approaches. In this regard, it is noteworthy that pairing adjunctive psychological interventions that focus on changing so-called *cognitive appraisal strategies* (described below) of the individual with behavioral interventions (i.e., those aimed at achieving weight loss through exercise and dietary changes) appears to be efficacious in remediating adverse metabolic and cardiovascular risk profiles—while also promoting the maintenance of lifestyle changes—as compared with dietary and physical exercise interventions followed in isolation (Shaw, O'Rourke, Del Mar, & Kenardy, 2005). This suggests that the study of cognitive appraisal processes in association with MetS risk may benefit from further investigation for two reasons. The first reason is based on the apparently beneficial effects of adjunctive psychological interventions on cardiovascular disease risk reduction. The second is based on the need to better understand the biological and behavioral correlates of the MetS so that potentially common etiological factors relating to the clustering of cardiometabolic risk factors may be identified and targeted for prevention and intervention (Hjemdahl, 2002).

1.2 STRESS- AND AFFECT-RELATED CORRELATES OF THE METABOLIC SYNDROME: A POTENTIAL ROLE FOR EMOTION REGULATION

As stated previously, the MetS presents with a complex pathophysiology whose etiology is not well understood (Grundy, Brewer, Cleeman, Smith, & Lenfant, 2004; Miranda, DeFronzo, Califf, & Guyton, 2005). Various factors have been considered to account for the shared variance or clustering among MetS components, such as a proinflammatory state (Eckel, Grundy, & Zimmet, 2005; Gustafson, Hammarstedt, Andersson, & Smith, 2007; Marsland, McCaffery, Muldoon, & Manuck, 2010). Empirically, however, no single factor appears to account (entirely or exclusively) for the clustering of syndrome components (Mendez et al., 2010). Further, genome-wide association (GWA) studies have yet to clearly identify genetic factors that commonly account for the pathogenesis and joint expression of syndrome components (Joy, Lahiry, Pollex, & Hegele, 2008; Lusis, Attie, & Reue, 2008). In fact, the genes that have been identified through GWA studies account for ~5-10% of the variance of the MetS phenotype (Lusis et al., 2008). Against this background, the relative contributions of behavioral and environmental factors in explaining the development of the MetS have become increasingly studied. One such factor widely studied in this regard is psychological distress (Tamashiro, 2011), most often reflected by elevated or sustained levels of negative emotionality (or negative affect).

Indeed, psychological distress has been widely implicated in the etiology of the MetS and in the consequent elevation of CHD risk in particular (Brunner et al., 2002; Rozanski,

Blumenthal, & Kaplan, 1999; Vitaliano et al., 2002). In the main, prospective studies demonstrate that the incidence of the MetS and CHD is often preceded by prolonged periods of either mild and/or severe psychological distress, including general life stress, depressive and anxiety symptoms, and major depressive disorder (Chandola, Brunner, & Marmot, 2006; Goldbacher, Bromberger, & Matthews, 2009; Goldbacher & Matthews, 2007; Pyykkönen et al., 2010). And interestingly, experimentally-induced depressive symptoms in primates seem to suggest that the induction of distress through social subordination appears to be followed by the development of MetS components, as well as coronary artery atherosclerosis (Shively, Laber-Laird, & Anton, 1997). Additional apparent convergence between animal and human studies is found in studies showing that psychological distress is linked to functional disturbances in hypothalamic-pituitary-adrenal (HPA) axis activity, autonomic nervous system activity, and lipid metabolism in the context of the development of the MetS or MetS-like models (Brunner et al., 2002; Chrousos, 2000; Rosmond, 2005; Shively, Musselman, & Willard, 2009). In humans, for example, increased self-reported negative affect is associated with elevated fasting plasma glucose (Skaff et al., 2009), blood pressure (Kamarck et al., 1998), and circulating lipid and proinflammatory cytokine levels (Carroll et al., 2011; Steptoe, Hamer, & Chida, 2007; Wirtz, Ehlert, Bärtschi, Redwine, & von Känel, 2009). From these and other similar observations, it has been suggested that negative emotions and psychological factors, including depression, anxiety, and distress, may relate to risk for the MetS by impacting affect-related HPA axis functioning, autonomic activity, and possibly systemic inflammation. Hence, psychological distress may represent one of several possible etiological factors in the development of MetS risk.

Addressing the possible links between psychological distress and the MetS has prompted animal and human research on individual differences in coping or other regulatory processes that

might function to modulate negative affect. For instance, Roman Low Avoidance rats that exhibit apparent passive coping behaviors to behavioral stressors are more likely than control animals to develop insulin resistance and components of the MetS under comparable feeding conditions (Boersma, Scheurink, Wielinga, Steimer, & Benthem, 2009; Boersma, Benthem, van Dijk, & Scheurink, 2011; Boersma, Benthem, van Dijk, Steimer, & Scheurink, 2010). Work in humans has suggested that correlates of the MetS, such as elevated glycated hemoglobin (HbA_{1c}), are more prevalent among individuals who report engaging in low levels of active coping strategies, such as problem-solving, and who report low levels of perceived control over stressful situations (Feldman & Steptoe, 2003). Further, passive coping styles that are characteristic of avoidance and perceived lack of control have also been associated with increased prevalence of hypertension in humans (Opie, 2004). More specifically, in terms of risk for the MetS, Yancura, Aldwin, Levenson, & Spiro (2006) found that emotionally negative, stressful experiences that are met with positive coping strategies covary inversely with the presence of the MetS. Hence, self-regulatory strategies that comprise positive coping styles may protect against meeting criteria for the MetS. Interestingly, in that study, neither negative nor positive affect *per se* related to the presence of MetS. In light of prior work highlighting the differential associations of various coping styles with physical health outcomes, Yancura et al. (2006) interpreted their findings to suggest that the affect modulation that results from emotion regulation could play a role in linking adaptive coping and the MetS. Thus, this kind of evidence suggests that the observed relation of psychological distress to the MetS in prior studies may relate in part to a reduced capacity to adaptively regulate negative emotional states, as opposed to the mere experiences of such states.

This particular view has been encompassed in recent theoretical models of emotional flexibility that suggest that individuals who are able to flexibly regulate their emotions exhibit more favorable physical health outcomes and reduced CHD risk (Kubzansky, Park, Peterson, Vokonas, & Sparrow, 2011; Kubzansky & Thurston, 2007; Rozanski & Kubzansky, 2005). In this regard, flexibility models expand upon the pathways that may link negative emotions or psychological distress and risk for MetS by incorporating the notion that the ineffective *regulation* of negative emotional experiences might also impact MetS pathophysiology and, consequently risk for CHD and other related outcomes. Hence, existing work and theoretical models would appear to suggest that individual differences in the ability to employ adaptive emotion regulation strategies to cope with negative emotional states and reduce psychological distress may increase vulnerability to physical illnesses, such as CHD, as conferred by the MetS.

1.3 WHAT IS EMOTION REGULATION AND HOW MIGHT IT RELATE TO THE METABOLIC SYNDROME?

The mechanisms linking emotion regulation to aspects of physical health, including MetS and CHD risk, can be viewed from a process model of emotion regulation (Gross & Thompson, 2007; Gross, 1998). According to this model, emotion regulation can be construed as the modifying of an emotional response through a set of automatic and control processes (Gross & Thompson, 2007; Gross, 1998). More precisely, these control processes are guided by goals that either focus on *cognitive change* or *behavioral control*. Moreover, this distinction of emotion regulation into cognitive change and behavioral control strategies has possible consequences for

physical health outcomes that are associated with sustained patterns of negative affect and autonomic physiology (Gross & John, 2003; Gross, 1998). Two control strategies that are relevant in this regard are cognitive reappraisal and behavioral suppression.

Cognitive reappraisal is one of the most commonly studied emotion regulation strategies that reflect cognitive change processes. As such, cognitive reappraisal involves altering how a situation is interpreted in order to change the emotional meaning and ensuing experiential, expressive, and physiological responses associated with the emotion response (Gross, 1999; Lazarus & Alfert, 1964). This emphasis on changing how one thinks about the emotional relevance of a situation is consistent with appraisal theories of emotion and stress, which contend that appraisals are essential in generating emotional states and the concurrent physiological changes that accompany emotional responses (Lazarus & Folkman, 1984; Lazarus, 1966). Moreover, because the generated emotional responses are dependent on the cognitive appraisal of the situation, it is likely that emotional responses should be amenable to change via cognitive reappraisal strategies. For this reason, cognitive reappraisal is generally conceptualized as an *antecedent-focused* emotion regulation strategy whereby regulatory processes are typically employed prior to the onset of an emotional response (see Figure 1; Gross & Thompson, 2007; Gross, 1998). Hence, in keeping with the temporal course of an emotion response, cognitive reappraisal strategies target the emotion appraisal period that occurs early in the emotion generation process. This reconstrual of an emotion-eliciting situation furthers the notion that employing cognitive reappraisal strategies during negative emotional experiences could attenuate the presumably adverse components of the multisystem emotion response (experience, expression, physiology) that often follows negative affect (Gross & John, 2003; Gross, 1998).

A large body of experimental studies provides support for the putatively adaptive function of cognitive reappraisal. In a recent meta-analysis, it was concluded that instructed use of reappraisal strategies consistently decreases the self-reported experience and behavioral expression of negative emotions (Webb, Miles, & Sheeran, 2012). Additional work has shown that the presumably salutary effects of instructed reappraisal are consistent with the results of studies that have examined the *spontaneous* use of emotion regulation strategies from an *individual-difference* standpoint. For instance, Egloff, Schmukle, Burns, & Schwerdtfeger (2006) reported that individuals who spontaneously use reappraisal strategies during a stressful public speaking task experienced less negative affect, showed less behavioral expression of anxiety, and demonstrated minimal arousal of autonomic physiology. More recent work from Memedovic, Grisham, Denson, & Moulds (2010) also suggested that individual differences in the trait-like use of reappraisal are associated with reduced self-reported anger and blood pressure reactivity following anger provocation, which might be linked to the beneficial effects that cognitive reappraisal might afford to individuals when they are faced with anger-inducing situations (Denson, Grisham, & Moulds, 2011). Moreover, trait-like use of cognitive reappraisal is related to decreased negative affect, as well as a decreased cardiovascular and neuroendocrine responsiveness to psychological distress (e.g., Carlson, Dikecligil, Greenberg, & Mujica-Parodi, 2012; Mauss, Cook, Cheng, & Gross, 2007). Thus, it would appear plausible that reappraisal as a cognitive emotion regulation strategy might relate to MetS risk via buffering effects along psychological distress, autonomic, and neuroendocrine pathways (Brunner et al., 2002; Chrousos, 2000).

In contrast to cognitive change and reappraisal strategies, behavioral control strategies, including expressive suppression, involve efforts to control or inhibit ongoing emotion-

expressive behavior without affecting emotional experience (Gross & Levenson, 1993; Gross, 2002). Since expressive suppression is defined as *response-focused* strategy, this emotion regulatory process is implemented after the various emotion response components have been initiated with the goal of impacting only the behaviors associated with emotional responses. However, an emphasis on down-regulating negative emotions through suppression may not be an adaptive emotion regulation strategy (John & Gross, 2004). For example, it has been suggested that suppressing outward signs of negative emotional experiences often results in *increases* in peripheral physiological activity (e.g., increases in sympathetic nervous system outflow), which over time if repeated often may relate to adverse cardiovascular and other health outcomes (Gross & Levenson, 1993, 1997; Harris, 2001; Webb et al., 2012).

Given the potentially divergent consequences of cognitive reappraisal and behavioral suppression on emotional responding, particularly physiological responding, it is possible that the tendency to differentially use these emotion regulation strategies could relate to physical health outcomes (John & Gross, 2004). In fact, psychophysiological studies of emotion regulation provide a basis to speculate whether typical use of cognitive reappraisal or suppression would be associated with differential risk (Gross, 1998). That is, the tendency to use cognitive reappraisal might relate to physiological changes that are 'metabolically adaptive', at least with respect to coping with a given psychological stressor or negative emotional situation (e.g., Mauss et al., 2007). Consistent with this hypothesis, Kinnunen, Kokkonen, Kaprio, & Pulkkinen (2005) reported prospective evidence that dispositional use of cognitive strategies to regulate negative emotions related to decreased risk for the development of the MetS. In contrast, it is conceivable that typical suppression use could relate to increased risk for MetS and associated components possibly via repeated increases in sympathetic cardiovascular outflow

during negative emotional situations. For instance, evidence suggests that the tendency to suppress emotion-expressive behavior during periods of increasingly high levels of negative affect predicts MetS factors, such as hypertension and incident CHD (Mauss & Gross, 2002). Greater use of suppression in everyday life has also been observed among women who are morbidly obese relative to healthy controls (Zijlstra et al., 2012). Moreover, among patients with coronary artery disease, intense negative emotions are associated with poorer physical functioning among individuals who made greater use of behavioral suppression (Karademas, Tsalikou, & Tallarou, 2011). These lines of evidence mirror recent prospective, longitudinal studies that consistently show that poor emotion regulation, self-regulation, and inhibitory control skills during early childhood determined the onset of weight problems in childhood and adolescence (e.g., Duckworth, Tsukayama, & Geier, 2010; Graziano, Calkins, & Keane, 2010). Together, these studies suggest that individual differences in cognitive (i.e., reappraisal) and/or behavioral (i.e., suppression) emotion regulation strategies may reflect trait-like characteristics that relate to MetS risk and its components.

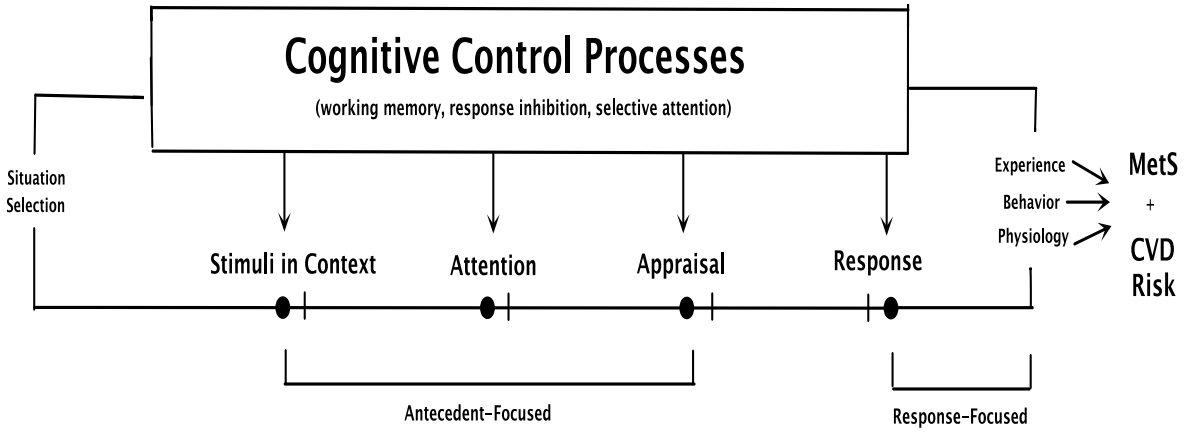

Figure 1. The process model of emotion and emotion regulation

The diagram outlines the steps involved in generating an emotion and how cognitive control processes can be implemented at each stage to regulate the emotion-generation process. How cognitive control processes interact with each emotion-processing step will differentially influence the multisystem emotion response (experience, behavior, physiology) and subsequent risk for MetS and CVD.

1.4 WHAT BRAIN AREAS MIGHT LINK COGNITIVE REAPPRAISAL WITH THE METABOLIC SYNDROME?

Although prior studies support the notion that cognitive and behavioral types of emotion regulation may be differentially associated with adverse cardiovascular outcomes, including obesity, hypertension, and the MetS, further work is needed to characterize the various processes by which emotion regulation is related to physical health (John & Gross, 2004). For example, autonomic and neuroendocrine responses during the regulation of negative affect have been proposed as mechanisms that may link cognitive emotion regulation strategies to the MetS (Kinnunen et al., 2005). However, it is possible that the autonomic differences that characterize cognitive reappraisal and suppression strategies may be secondary to functional changes in the central nervous system. Indeed, there is evidence that the cognitive and behavioral response processes involved in emotion regulation in addition to the associated autonomic measures of emotional responding are governed by partially overlapping brain systems. More precisely, prefrontal and cingulate brains regions that are networked with one another can regulate autonomic and neurohormonal outflow through circuitry with midbrain and brainstem areas that are more proximally involved in monitoring and controling peripheral physiology (Dampney, 1994; Loewy, 1991; Neafsey, 1990). At the same time, these prefrontal and cingulate brains regions are involved in supporting higher cognitive control processes (e.g., working memory maintenance and manipulation, response inhibition, set-shifting, performance monitoring; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004) that are relevant to the cognitive control

of emotions as well as controlling emotional coping behaviors (Ochsner & Gross, 2008; Phillips, Ladouceur, & Drevets, 2008). In this regard, prefrontal and cingulate systems are viewed as components of a neural network involved in the integration of autonomic, affective and cognitive control processes that facilitate both evaluative and effortful emotion regulation strategies, such as cognitive reappraisal and suppression (Critchley, 2009; Phillips et al., 2008). However, it remains to be determined whether these same prefrontal and cingulate brain systems that coordinate and integrate cognitive control processes with physiological activity to support emotion regulation link differential use of emotion regulation strategies (i.e., reappraisal, suppression) to the MetS. Hence, there is a need to elucidate the neurobiological substrates that could potentially link specific types of emotion regulation and cardiovascular health outcomes (DeSteno et al., in press).

In support of this possibility, recent neural models of emotion regulation indicate that emotion regulation, particularly cognitive reappraisal, recruits executive cognitive control processes that are presumptively supported by regions of prefrontal (PFC) and anterior cingulate cortices (ACC; Botvinick, Cohen, & Carter, 2004; D'Esposito, Postle, & Rypma, 2000; MacDonald, Cohen, Stenger, & Carter, 2000; Ochsner & Gross, 2005; Ridderinkhof & van den Wildenberg, 2005). In the context of emotion, these cognitive control systems modulate limbic regions, including the amygdala and insula, which are implicated in emotional generative processes (Ochsner & Gross, 2005, 2008). In particular, cognitive reappraisal is thought to involve the dynamic interaction between these cognitive control and appraisal systems to restructure, implement, and maintain alternative response tendencies to emotional events. Moreover, these cognitive control systems are also involved in autonomic, neuroendocrine, and cardiovascular regulation, particularly in the context of engaging in effortful cognitive processes

(Buchanan et al., 2010; Gianaros et al., 2005; Gianaros, Jennings, Sheu, Derbyshire, & Matthews, 2007; King et al., 2009; Urry et al., 2006), which is consistent with concurrent physiological patterns of activity that are associated with the use of different emotion regulation strategies. In light of these integrative functions in mediating cognitive reappraisal and physiological activity, we elaborate below on the functional roles of particular control systems in jointly *(i)* coordinating autonomic and neuroendocrine activity with adaptive behavior and *(ii)* orchestrating the selection, implementation, and monitoring of reappraisal processes and strategies.

1.4.1 Medial Prefrontal Cortex

Prior research suggests a role for medial PFC (mPFC) in appraisal processes and in the inhibitory control of emotional behavior that is coordinated with adaptive decision-making, specifically through affective self-reflection (Gusnard, Akbudak, Shulman, & Raichle, 2001; Ochsner et al., 2004; Rudebeck, Bannerman, & Rushworth, 2008). Consistent with this, animal studies have confirmed that mPFC is essential for inhibiting behavioral fear responses in view of the fact that stimulating mPFC neurons gates fear acquisition that is mediated through several amygdala nuclei (Quirk, Likhtik, Pelletier, & Paré, 2003). Similarly, neuropsychological patients with selective damage to the mPFC exhibit a lack of behavioral control during stressful events and deficits in regulating their emotions, perhaps indicating that a conscious, internal representation of one's emotional state may be important for adaptive reappraisal of negative affect (Buchanan et al., 2010). Additional studies have shown a reliable, early recruitment of mPFC when reappraising negative emotions and down- regulating amygdala and insula activity (Etkin, Egner, & Kalisch, 2011; Goldin, McRae, Ramel, & Gross, 2008; Ochsner et al., 2004). This

involvement in modulating affective responses to stressful or otherwise emotionally-evocative experiences is consistent with mPFC circuitry—particularly its bidirectional connections with subcortical brain systems, including the amygdala and insula, and its connections with dorsolateral PFC (DLPFC) regions that are critical in the effortful maintenance, manipulation, and interpretation of affective and cognitive stimuli and information in working memory (Carmichael & Price, 1995; McDonald, Mascagni, & Guo, 1996; Ochsner, Bunge, Gross, & Gabrieli, 2002; Price, 2005). Partly as a result of the inhibitory control that the mPFC can broadly exert over subcortical systems involved in fear conditioning, several subregions of the mPFC also exhibit a capacity to inhibit autonomic and HPA axis activity tied to psychological challenges and stressors (Ulrich-Lai & Herman, 2009). Indeed, mPFC lesion patients demonstrate increased heart rate responses to psychological stress, coupled with heightened negative affect and threat-perceptions (Buchanan et al., 2010; Critchley et al., 2003), which suggests the mPFC may be important for orchestrating physiological responses (i.e., dampened physiological arousal) that often appears to accompany cognitive reappraisal of negative affect (e.g., Mauss et al., 2007). Taken together, the mPFC is widely viewed as a neural substrate that helps coordinate appropriate autonomic responses during emotion generation and regulation (Silvers, Buhle, Ochsner, & Silvers, in press).

1.4.2 Lateral Prefrontal Cortex

Studies using functional neuroimaging methods have related cognitive control processes, such as actively maintaining and manipulating information in working memory, to the DLPFC (Cohen et al., 1997). From a reappraisal perspective, this suggests a possible role for the DLPFC in manipulating the affective representation of emotional stimuli (Ochsner & Gross, 2005), while

ventrolateral PFC (VLPFC) appears to be involved in the evaluation and selection of the emotional interpretation in accordance to reappraisal goals (Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008). Together, areas of the lateral PFC might be jointly involved in initiating goal-relevant strategies that cognitively adjust an emotional response and in sustaining these cognitive strategies over the course of the emotional experience. Critically, however, because the DLPFC does not project directly to emotional appraisal systems, such as the amygdala, this crosstalk with the VLPFC and mPFC is thought to be important in the 'top-down' modulation of emotion response tendencies (Urry et al., 2006).

1.4.3 Dorsal Anterior Cingulate Cortex

Areas within the dorsal ACC (dACC) are thought to support attention, executive control, and conflict and error monitoring (Botvinick et al., 2004), as instantiated by reciprocal circuitry with the lateral PFC (BAs 9/46), motor and supplementary motor cortex (BAs 4/6), and parietal cortex (BA 7). At a broader level, this cortico-cortical circuitry with frontoparietal control regions positions the dACC to initiate and maintain cognitive control (Bush, Luu, & Posner, 2000). Moreover, dACC areas support appraisal and regulation processes that are coordinated with physiological activity (Gianaros & Sheu, 2009; Gianaros et al., 2005). Consistent with this, it has been speculated that areas within the dACC calibrate and regulate the magnitude of autonomic reactions to self-relevant demands in order to support adaptive cognitive coping processes (Gianaros & Sheu, 2009; Gianaros et al., 2005; Gianaros, Onyewuenyi, Sheu, Christie, & Critchley, 2012). In fact, lesions to the dACC have been shown to alter cardiac responses when individuals are performing increasingly demanding cognitive tasks (Silvers et al., in press). Although there is evidence that both cognitive and affective coping processes recruit the dACC

in order to monitor ongoing conflict that involve overcoming incongruent, prepotent response tendencies (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Ochsner, Hughes, Robertson, Cooper, & Gabrieli, 2009), indicating a role of the dACC in integrating potentially distressing emotional and cognitive stimuli (Allman, Hakeem, Erwin, Nimchinsky, & Hof, 2001; Bush et al., 2000). Similarly, in the context of cognitive reappraisal, dACC may function as a conflict monitoring system to ensure reappraisal success by monitoring for conflicts between initial emotion appraisals and subsequent cognitive reappraisals (Ochsner et al., 2002).

1.5 GOALS AND HYPOTHESES OF THE PRESENT STUDY

The converging literature reviewed above show that the neural systems involved in emotion regulation—particularly cognitive reappraisal strategies—have been well defined across several cognitive neuroscience studies. More importantly, the functional properties of these prefrontal and cingulate cognitive control systems agree with neuropsychological studies demonstrating that reappraisal relies on higher cognitive control abilities, such as working memory capacity (Ochsner & Gross, 2005). In point, cognitive control capacity is of particular importance to reappraisal as it constrains the degree to which an individual may successfully reframe emotional events in a manner compatible with the regulatory end goal (Schmeichel, Volokhov, & Demaree, 2008). Interestingly, individuals with the MetS show impairments in these supportive cognitive control abilities, including working memory and executive function, reappraisal strategies rely upon (Akbaraly et al., 2010; Bokura, Nagai, Oguro, Kobayashi, & Yamaguchi, 2010; Cavalieri et al., 2010; Kumari, Brunner, & Fuhrer, 2000; Yaffe, 2007). More importantly, these cognitive control impairments in the MetS have been shown to covary with microstructural damage in

prefrontal cortical areas (Segura et al., 2010; Yates, Sweat, Yau, Turchiano, & Convit, 2012) in addition to decreased activation in the mPFC during a 2-back verbal working memory (Hoth et al., 2011). As such, individual differences in neural activity in so-called cognitive control regions of the brain that support executive functions and by extension cognitive reappraisal, could plausibly covary with presence of the MetS. However, little is known about how these cognitive control neural systems differ between individuals with and without the MetS, particularly in the context of cognitive reappraisal.

In view of the above, we thus reason that functional variation in the prefrontal and cingulate neural systems that support both cognitive control and peripheral physiology may link dispositional reappraisal and the MetS. Several studies provide initial evidence supporting this speculation. First, prospective and longitudinal studies have shown that individual differences in cognitive emotion regulation abilities predict the presence of MetS and associated syndrome components (Graziano et al., 2010; Kinnunen et al., 2005). Second, recent work has also shown that frequent cognitive reappraisal use in everyday life is related to increased dACC and DLPFC activity when inhibiting proponent responses to negative emotional material (Vanderhasselt, Baeken, Van Schuerbeek, Luypaert, & De Raedt, 2013). Moreover, self-reported use of cognitive reappraisal is associated with increased activation in frontoparietal cognitive control regions during the processing of negative emotional stimuli (Drabant, McRae, Manuck, Hariri, & Gross, 2009). Third, individuals with the MetS demonstrate decreased activity in similar frontoparietal brain areas during a verbal working memory task (Hoth et al., 2011). Moreover, these cognitive control prefrontal and cingulate regions are networked with midbrain and brainstem areas to regulate autonomic, neuroendocrine, and cardiovascular activity that is relevant to both emotion regulation processes and the pathophysiology of the MetS. Synthesizing these findings, the

present study proposes a first step towards identifying a specific neurobiological pathway that relates trait reappraisal to the MetS. Specifically, we attempt to test whether cognitive control neural systems show altered patterns of activation during a cognitive conflict task (i.e., Stroop color-word interference task) among individual with the MetS, and whether this functional variation in cognitive control neural systems represents a neurobiological pathway through which trait reappraisal covaries with the MetS.

Based on available literature, the following hypotheses were tested. First, we tested whether the tendency to use cognitive reappraisal in daily life is inversely related to the presence of the MetS, the number of MetS criteria met across individuals, and a derived continuous MetS score.[1] Second, we used functional magnetic resonance imaging (fMRI) to test the hypothesis that the tendency to use cognitive reappraisal is related to increased activation within neural systems implicated in cognitive control. To this end, otherwise healthy middle-aged adults performed a modified version of the Stroop color-word interference task, which requires cognitive control, evokes a negative emotional state, and engages prefrontal and cingulate brain areas (Sheu, Jennings, & Gianaros, 2012). Next, we tested the third hypothesis that individuals with the MetS would exhibit decreased activation in the neural areas implicated in cognitive control noted above. Lastly, we tested whether differential neural response in the above cognitive control brain areas partly account (partially mediates) for cross-sectional associations between tendency to use cognitive reappraisal and the MetS.

[1] The MetS was operationally defined as *(i)* the presence of the MetS; *(ii)* the number of syndrome criteria met; and *(iii)* a continuous MetS score (see Section 2.3 in Methods). Additional aims examining the relation of the MetS with emotion regulation and brain activity within cognitive control regions tested these three definitions of the MetS.

1.5.1 Exploratory Hypotheses

Two additional hypotheses were tested. First, we tested whether the incongruent Stroop condition modulated the functional connectivity of the BOLD signal in the dACC and DLPFC network. And second, we examined whether these temporally coupled BOLD signal changes in the dACC and DLPFC covaried with self-reported reappraisal use and the MetS. These hypotheses were explored based on current understanding of the functional interactions and neuroanatomical connections between these two cortical brain regions in regulating cognitive control processes, including response inhibition, decision-making, performance monitoring, and initiating compensatory behavioral adjustments in order to select among competing cognitive responses (Sallet et al., 2011). Hence, these two regions within prefrontal and cingulate cortices that support various aspects of cognitive control are known to exert influence over each other based on context-specific situations. The dACC shows extensive connectivity to DLPFC as well as motor cortices, which furthers the dACC importance in implementing control processes for task goals, and coordinating motor behavior to accomplish these goals given its cortico-cortical connectivity with cogntive control and motor pathways (Paus, 2001). Meta-analyses of human functional neuroimaging studies further indicate that the ACC plays a key role in executive control (Bush et al., 2000), with emerging evidence demonstrating the functional coactivation between dACC and DLPFC during cognitive control tasks, such as the Stroop color-word task, that demand selective attention, performance monitoring, and interference resolution (Mohanty et al., 2007; Nee, Wager, & Jonides, 2007; Ridderinkhof et al., 2004)

Several control models have proposed that the functional relationship of the dACC and DLPFC in implementing hierarchical levels of cognitive control can be understood from a conflict monitoring perspective (Botvinick et al., 2004). According to this conflict model of

cognitive control, dACC is thought to monitor performance, evaluate actions, and detect response conflicts within these performed actions. In the event of conflict, dACC signals the need for behavioral adaption by recruiting DLPFC regions that exert attentional control to maintain representations of goal-directed behavior as it pertains to a task. This hypothesis was recently supported by evidence indicating that increased conflict-related activity in the dACC during incongruent trials of the Stroop task predicted greater DLPFC activity in subsequent incongruent trials (Kerns et al., 2004). Moreover, dACC was negatively associated with reaction time (RT) during these subsequent incongruent trials while DLPFC was related to slower RT on post-error trials. In light of these results, it is possible that functional interactions between prefrontal and cingulate brain regions that monitor performance and mediate adjustments in cognitive control may assume a similar role among individuals who generally use cognitive reappraisal to reevaluate the affective salience of a negative situation (Ochsner et al., 2002; Ochsner & Gross, 2005; Phillips et al., 2008). That is, the need to reappraise a negative emotional event in unemotional terms requires *(i)* generating a strategy to minimize negative appraisals, *(ii)* maintaining the reappraisal goal in mind as well as the new appraisal, and *(iii)* monitoring changes in emotional state that might be due to interference from the enduring negative appraisals of the emotional event. These cognitive processes underlying reappraisal are presumably implemented by medial and lateral regions of prefrontal cortical regions, including the dACC and DLPFC (Ochsner & Gross, 2005, 2008). Support for this cognitive control network in possibly mediating effective cognitive reappraisal comes from several reports. First, dACC has been shown to track not only task performance, but changes in subjective frustration and negative affect that accompany demanding, cognitive control tasks, such as the Stroop task (Spunt, Lieberman, Cohen, & Eisenberger, 2012). Second, increased dACC and DLPFC activity

has been associated with decreasing negative affect and self-reported craving for cigarettes (Kober et al., 2010; Ochsner et al., 2002; Phan et al., 2005; Zhao et al., 2012) due to reappraisal, which is consistent with the role of dACC in reducing RT on incongruent Strop trials (Kerns et al., 2004). On this basis, it is possible that individual differences in typical reappraisal use might recruit functionally coupled dACC and DLPFC activity that support non-affective forms of cognitive control during demanding, incongruent trials of the Stroop task (Ochsner & Gross, 2008).

2.0 METHODS

2.1 PARTICIPANTS

Participants were 155 otherwise healthy adults (78 men, 77 women; M age: 40.7 ± 6.2 SD years, range = 30-50 years) who were recruited through mass mailings to residents of Allegheny County, PA, USA. All participants were right-handed, fluent in English, in good general health, had normal or corrected-to-normal vision and also met the following inclusion criteria: had no history of (1) cardiovascular disease (including treatment for or diagnoses of hypertension, stroke, myocardial infarction, congestive heart failure, and atrial or ventricular arrhythmias); (2) prior neurosurgery or neurological disorder; (3) any current treatment for or self-reported psychiatric disorder; (4) typical consumption of more than 15 alcoholic beverages per week; (5) daily use of corticosteroid inhaler; (6) current use of psychotropic, lipid lowering, or any cardiovascular medication, including any medication to control blood pressure; (7) metal implants or exposure; and (8) claustrophobia. Women were excluded if pregnant (as verified by urine test). The ethnicity of the sample was Caucasian/White (70.3%), African American/Black (21.9%), Asian (5.8%), and multiracial or other (1.9%). All participants provided informed consent prior to completing study protocols, which were approved by the University of Pittsburgh Institutional Review Board.

All analyses for this thesis were based on data from 139 subjects (74 men, 65 women). This reduced sample size was due to missing variables needed to compute MetS criteria (n = 3) and missing or poor quality functional neuroimaging data (n = 13). These excluded participants (4 men, 12 women) did not differ from the final sample with respect to emotion regulation measures (described below) or MetS-related measures. However, there was a trend for the excluded subjects to be slightly older, t (153) = -1.89, p = 0.06; M = 43.44 ± 5.0 SD vs. M = 40.39 ± 6.2 SD years. The excluded individuals were largely Caucasian/White (n = 7) and African American/Black (n = 8), with one individual identifying their ethnicity as 'Other'.

2.2 STUDY PROTOCOL

All study participants completed three separate assessment protocols that were completed over 3 visits. However, only data from the first two visits (i.e., session 1 and 2) were used to test the aims of this thesis.

For session 1, participants completed measures that documented their medical histories, demographics, and health behaviors. For session 2, participants arrived at the scanning facility between the hours of 7:00AM and 11:00am in a fasted stated. Before this fMRI session, participants refrained from eating, exercising, and consuming tobacco and caffeinated products for 8 h, and drinking alcohol for 12 h prior to this session. Upon arrival, participants were assessed for anthropometric measures, fasting blood chemistries, and seated BP. Participants then completed the fMRI protocol where data was collected on the Stroop color-word interference task. After the fMRI protocol, participants completed several psychosocial measures, important among them was the Emotion Regulation Questionnaire.

2.3 BEHAVIORAL AND PHYSIOLOGICAL ASSESSMENTS

2.3.1 Emotion Regulation Questionnaire

Individual differences in the typical use of emotion regulation strategies were assessed with the Emotion Regulation Questionnaire (ERQ; Gross & John, 2003). The ERQ was administered on the second visit after participants had completed the neuroimaging protocol. The ERQ is comprised of 10-items, each using a 7-point scale (1 = strongly disagree and 7 = strongly agree). Six items assess the tendency to use cognitive reappraisal, while the other four items assess habitual use of suppression, with scoring for each subscale determined on the mean of the items. There is evidence indicating that the two strategies are distinct (Gross & John, 2003), with a more recent factor analysis demonstrating that cognitive reappraisal and suppression utilization are independent constructs (Moore, Zoellner, & Mollenholt, 2008). In support of this, within this sample, the two emotion regulation strategies were not correlated, r = -0.08, p = 0.33. The scales for the two strategies also exhibit reasonable internal consistency (reappraisal, α = 0.79; suppression, α = 0.73) and acceptable test-retest reliability (α = 0.69 for both scales; Gross & John, 2003) as well as independence from general intelligence (Gross & John, 2003). Moreover, consistent with prior work (Drabant et al., 2009; Gross & John, 2003), participant's ERQ reappraisal and suppression use scores did not correlate with verbal IQ as estimated by the National Adult Reading Test-Revised (NART-R; ps > 0.49).

2.3.2 Assessment of the Metabolic Syndrome

Participants arrived for a neuroimaging protocol (i.e., Session 2) between 7:00AM and 11:00AM, after an 8-hour fast. The fast also included abstaining from exercising and consuming caffeine, alcohol, and tobacco products. Prior to neuroimaging, participants' provided a seated, resting BP that was measured from the non-dominant arm with an oscillometric device (Critikon Dinamap 8100, Johnson & Johnson, Tampa, FL). Participants provided 3 BP readings taken 2 min apart after a ~20 min acclimation period, with the average of the last 2 of the 3 BP readings being used to compute resting systolic (SBP) and diastolic (DBP) blood pressures. Participants' waist circumference (in inches) was measured at the level of the umbilicus to the nearest ½ centimeter at end expiration. After each participant's height, weight, and waist circumference were measured, a research nurse performed blood draws. Procedures to determine fasting serum lipids and glucose levels were performed in the Department of Primary Care Laboratory Services (Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center). Concentrations of total cholesterol and triglycerides were measured by a CHOL and triglyceride GPO reagent, respectively, using an enzymatic, timed-endpoint method on the SYNCHRON LX System (Beckman Coulter, Inc., Brea, California; Allain, Poon, Chan, Richmond, & Fu, 1974; Bucolo & David, 1973; Pinter, Hayashi, & Watson, 1967; Roeschlau, Bernt, & Gruber, 1974; Trinder, 1969). The concentration of high-density lipoprotein (HDL) cholesterol was measured with a HDLD reagent on the SYNCHRON LX System, which uses an enzymatic, time-endpoint method to uniquely facilitate a detergent that solubilizes only the HDL lipoprotein particles (Beckman Coulter, Inc., Brea, California; Allain et al., 1974; Roeschlau et al., 1974). Low-density lipoprotein (LDL) cholesterol concentrations were estimated by using the Friedewald calculation (Friedewald, Levy, & Fredrickson, 1972).

The MetS was defined by the criteria of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (Grundy et al., 2004; "Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report," 2002). According to NCEP criteria, the MetS is defined as the presence of three or more of the following: (1) serum triglycerides > 150 mg/dL; (2) fasting serum glucose > 110 mg/dL; (3) waist circumference > 102 cm in men or > 88 cm in women; (4) SBP > 130 or DBP > 85 mm Hg; (5) serum HDL cholesterol < 40 mg/dL in men or < 50 mg/dL in women.

Based on these criteria, the final sample included 22 individuals who met criteria for having the MetS and 117 who did not. As follows, the prevalence of the MetS in this study population was 15.8%, which is consistent with expected rates of the MetS demonstrated in national samples and similar community samples recruited from Allegheny County, Pennsylvania (Manuck, Phillips, Gianaros, Flory, & Muldoon, 2010; Muldoon et al., 2004, 2006). Among the 22 *with* the MetS, the following frequencies were observed across syndrome components: low HDL cholesterol (n = 21), elevated waist circumference (n = 19), elevated systolic (n = 12) and diastolic (n = 6) blood pressure, elevated triglycerides (n = 11), and elevated fasting glucose (n = 8). Among the 117 *without* the MetS, the following frequencies were observed across syndrome components: low HDL cholesterol (n = 38), elevated waist circumference (n = 25), elevated systolic (n = 15) and diastolic (n = 12) blood pressure, elevated triglycerides (n = 6), and elevated fasting glucose (n = 6). Across the entire sample, 47 participants met 0 MetS criteria, 44 met 1 criterion, 26 met 2 criteria, 17 met 3 criteria, 3 met 4 criteria, and 2 met 5 criteria. Table 1 shows descriptive information about the participants' demographic and health-related characteristics.

Table 1. Summary of participant characteristics

	Full sample (n = 139)	Individuals meeting NCEP MetS criteria (n = 22)	Individuals not meeting NCEP MetS criteria (n = 117)
Age, yrs	40.4 ± 0.5	40.2 ± 1.4	40.4 ± 0.6
Sex, m/f	74/65	12/10	62/55
Smoking status, never/former/current	93/26/20	13/4/5	80/22/15
Education, yrs	17.3 ± 0.3	17.0 ± 0.6	17.4 ± 0.3
Systolic BP, mmHg**	121.0 ± 0.9	128.6 ± 1.9	119.6 ± 0.9
Diastolic BP, mmHg**	73.7 ± 0.8	78.4 ± 2.1	72.9 ± 0.8
MAP, mmHg**	92.0 ± 0.8	97.9 ± 1.9	90.9 ± 0.8
BMI, kg/m^2**	27.1 ± 0.4	32.3 ± 1.0	26.2 ± 0.4
Waist, cm**	35.6 ± 0.4	41.4 ± 0.7	34.5 ± 0.4
Hip, cm**	41.8 ± 0.3	45.2 ± 0.7	41.1 ± 0.3
Triglycerides, mg/dL [b]**	75.0 (62.0)	147.0 (106.0)	70.0 (41.0)
HDL cholesterol, mg/dL**	49.7 ± 1.4	37.1 ± 1.0	52.1 ± 1.6
Glucose, mg/dL [b]**	87.0 (12)	96.0 (20.0)	86.0 (12.0)
Insulin, uIU/mL [b]**	7.0 (7.0)	11.0 (6.0)	5.0 (8.0)
C-reactive protein, mg/dL [b]*	0.14 (0.2)	0.23 (0.6)	0.12 (0.2)
ERQ Reappraisal**	31.7 ± 0.5	28.3 ± 1.4	32.3 ± 0.5
ERQ Suppression	13.5 ± 0.4	12.6 ± 0.9	13.7 ± 0.4
Task accuracy (% correct ± SD)			
Stroop congruent condition	84.7 ± 8.0	83.5 ± 8.4	85.0 ± 7.9
Stroop incongruent condition	56.3 ± 8.5	56.1 ± 8.2	56.4 ± 8.6
Task reaction time (ms)			
Stroop congruent condition	1278.9 ± 274.9	1267.0 ± 277.7	1281.2 ± 275.5
Stroop incongruent condition	1811.7 ± 420.1	1793.5 ± 411.0	1815.1 ± 423.5
Subjective Ratings (± SD)			
Baseline – valence	6.4 ± 1.5	6.2 ± 1.5	6.5 ± 1.5
Post Stroop – valence	4.8 ± 1.8	4.8 ± 1.6	4.8 ± 1.8
Baseline – arousal	2.8 ± 1.8	2.4 ± 1.6	2.8 ± 1.9
Post Stroop – arousal	5.9 ± 1.8	5.9 ± 1.7	5.8 ± 1.9
Baseline – control	6.1 ± 2.2	6.4 ± 1.9	6.1 ± 2.2
Post Stroop – control	4.1 ± 1.9	3.7 ± 1.9	4.2 ± 1.9

Note. BP = blood pressure; MAP = mean arterial pressure; BMI = body mass index; HDL = high-density lipoprotein; ERQ = Emotion Regulation Questionnaire. Values are mean ± standard error of the mean, unless indicated otherwise.

a Values are mean ± standard error of the mean, unless indicated otherwise.

b Median (interquartile range).

** $p < 0.05$; * $p < 0.10$

2.3.3 Assessment of Continuous Metabolic Syndrome Score

The most common conceptualization of the MetS in epidemiological studies is based on a binary definition that indicates presence or absence of the syndrome (i.e., coded presence = 1, absence = 0; Grundy et al., 2004). Despite clinical advantages of this binary approach to characterizing the MetS, the multiple definitions and criteria for the syndrome hinders direct comparison of findings across studies (Kahn, Buse, Ferrannini, & Stern, 2005). However, recent guidelines from the American Diabetes Association and the European Association for the Study of Diabetes (Kahn et al., 2005) recommend a continuous MetS score that overcomes certain methodological and conceptual limitations: *(i)* dichotomizing the continuous syndrome components introduces the loss of measurement precision, attenuates statistical power, and in some instances increases risk for Type I errors in multivariable models (Altman & Royston, 2006; Babyak, 2004; MacCallum, Zhang, Preacher, & Rucker, 2002; Royston, Altman, & Sauerbrei, 2006); *(ii)* syndrome components (i.e., fasting glucose, dyslipidemia, blood pressure, and central adiposity) are inherently continuous CVD risk factors which negates the need to dichotomize them according to established diagnostic cutoffs (Kahn et al., 2005); and *(iii)* CVD risk increases markedly as individuals meet more criteria for the MetS, further reducing the need to dichotomize the MetS as presence or absence.

Various methods have been implemented to derive the continuous MetS score, including principal components analysis (PCA) and standardized residuals (Kahn et al., 2005). Although the former PCA methodology factors in the weighted contribution of each syndrome component to the latent factor (i.e., defined as the MetS), the inherent issue of weighting variability across study populations poses limitations on the generalization of these study-specific, PCA-derived weights. In light of this, we determined the cMetS score by standardizing the individual

syndrome components (i.e., waist circumference, HDL cholesterol, triglycerides, BP, fasting glucose). The standardized BP measure was based on mean arterial pressure (MAP) since independently factoring in SBP and DBP would bias the cMetS score with two measures of BP. Additionally, the standardized HDL cholesterol values were multiplied by -1 due to the inverse association between HDL cholesterol and CVD risk. The standardized residuals (i.e., z-scores) for the five syndrome components were summed to create the continuous MetS score. Higher continuous MetS score is indicative of a less favorable cardiometabolic profile.

2.3.4 fMRI Cognitive Control Paradigm

To probe brain activity in the prefrontal cognitive control network, participants were scanned while completing a modified performance-titrated Stroop color-word interference task, which has been found to reliably recruit brain regions involved in cognitive control processes (Gianaros & Sheu, 2009; Gianaros et al., 2005, 2008, 2007; Sheu et al., 2012). The Stroop task has been established as a useful tool for investigating the brain mechanisms that underlie the recruitment of cognitive control during instances of decisional conflict and psychological distress. Similarly, the variant of the Stroop employed in this study has been shown to consistently increase BOLD activation in prefrontal and cingulate cognitive control areas given that participants must process conflictual information, receive negative feedback, and make time-pressured responses to unpredictable and uncontrollable stimuli that collectively elicit subjective distress (Sheu et al., 2012). In this modified Stroop task, participants completed six blocks of color-word identification trials that lasts for 9 min 20 s and comprised two alternating conditions: a congruent condition and an incongruent condition (see Figure 2). Prior to beginning each condition, participants fixated on a crosshair that was variably displayed for 10-17 s period. This

fixation period was interleaved between each condition block. Following the fixation period, each blocked condition instructed participants to identify the physical color in which a target word is presented in by selecting one of the four identifier words presented in a row below the target word. The target word was visually centered and four identifier word choices were randomly ordered in one row at the bottom. Participants selected an identifier word choice by pressing one of the four corresponding buttons on a response glove (e.g., thumb button = identifier word on the extreme left; ring finger button = identifier word on the extreme right). The selected identifier word choice was outlined and participants were provided feedback on whether the selection was correct before the next trial. Incorrect selections were highlighted and the correct identifier word choice was indicated to participants. For the congruent condition, the target word was in a physical color that matched the meaning (e.g., the target word GREEN was printed in green). For the incongruent condition, first, the target word appeared in a color that was dissimilar from the target word (e.g., the target word GREEN printed in red), and second, all the identifier word choices appeared in colors that was different from the color of the identifier word choice named. Participants completed three blocks of each condition, with each block lasting for 52-60 s.

An added goal of the modified Stroop task was to control for individual differences in task performance. To this end, each participants accuracy at the target word identification was performance titrated to (and maintained at) ~60% during each incongruent condition by implementing a variable stimulus onset asynchrony (SOA) during the incongruent condition that adjusted the trial presentation times in 500 ms steps within a range of 1-5 s. Hence, participants demonstrating better performance accuracy within a given incongruent condition elicited shorter response time windows in which to select an identifier word; conversely, less accurate

performance lengthened response windows for participants to identify the target word. For the congruent condition, the SOA was fixed across all trials and was determined by the mean SOA of the preceding incongruent condition.

2.3.4.1 Performance and Subjective Ratings of fMRI Paradigm

During the fMRI paradigm, task accuracy was determined by computing the percentage of trials completed correctly. Task accuracy during the incongruent condition of the Stroop task was also assessed to ensure performance was titrated below 60% accuracy. As expected, post hoc analyses determined that mean accuracy across all participants during the incongruent condition was titrated at 56.34% (SD = 8.51). Additional performance change scores (i.e., reaction time) for Stroop task were computed by subtracting the congruent condition from the incongruent condition. This RT change score between the conditions provided a measure of Stroop interference effect (i.e., incongruent RT – congruent RT).

Subjective ratings of valence (1, very unhappy; 9 very happy), arousal (1, very calm; 9 very aroused), and perceived control (1, very little control; 9 very much control) were also assessed in the fMRI protocol after the baseline (prestressor) and stressor task periods. Based on these numerical ranges, participants completed a self-assessment manikin scale (Bradley & Lang, 1994) to report their subjective feelings about the baseline and stressor periods. Task-related change scores for these subjective ratings were computed by subtracting baseline ratings from stressor task (i.e., Stroop) ratings. Baseline rating values were included as covariates in all analyses examining the derived subjective change scores.

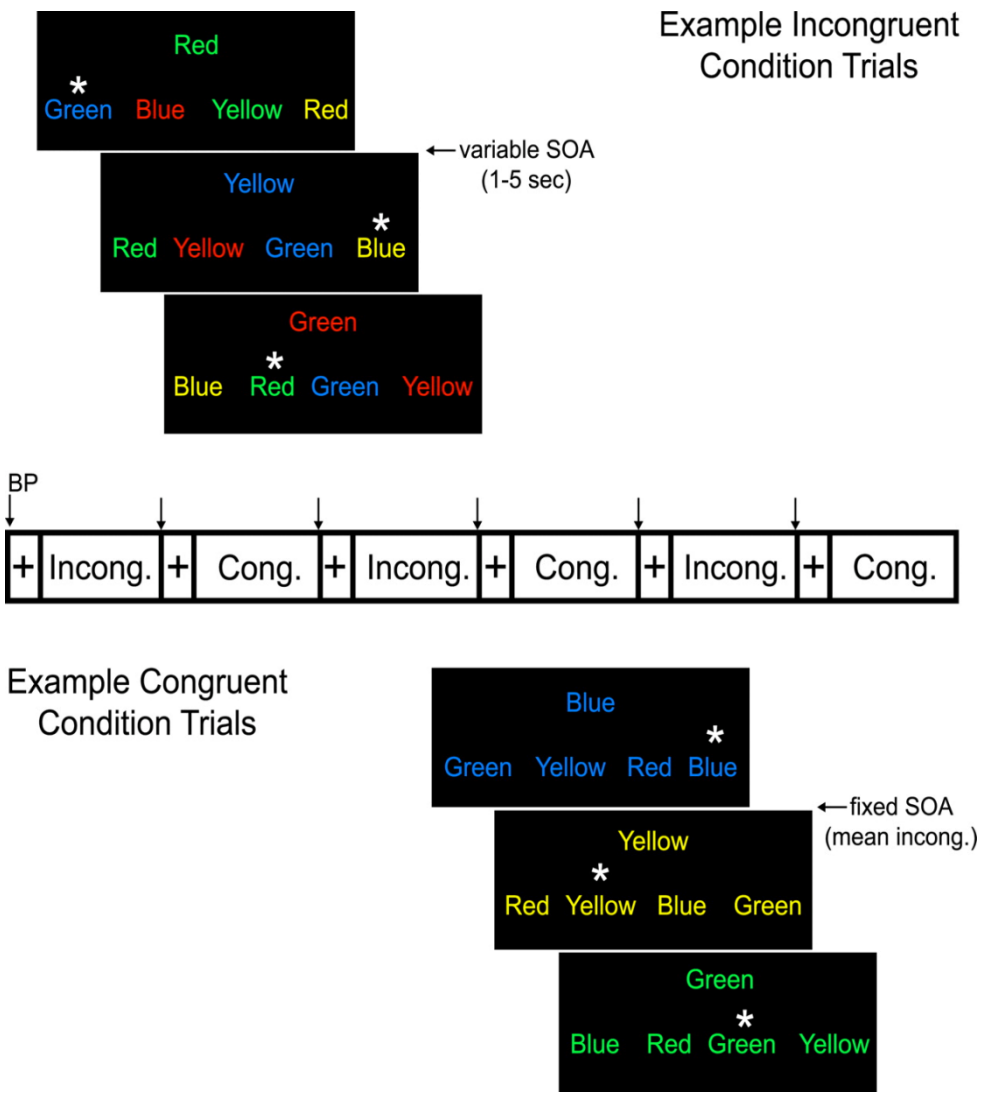

Figure 2. Visual schematic of the modified Stroop color-word interference task

The Stroop color-word interference task is a validated fMRI paradigm that engages cognitive control brain regions. The task had participants identify the color of the target word at the top of the screen during each trial by selecting one of the four answer choices below the target word. For illustration purposes, correct responses are indicated with a white asterisk above the word.

2.4 STATISCAL ANALYSIS

2.4.1 Demographic, Behavioral, and Cardiometabolic Variables

The presence or absence of the MetS was treated as a categorical variable in all analyses. Descriptive statistics were used to characterize participants *with* and *without* the MetS on several factors, including age, years of education, smoking status, Stroop task performance and subjective ratings, ERQ scores, and MetS components. These group differences were analyzed using ANOVA or *t* tests for continuous variables and χ^2 tests for categorical variables. Group characteristics are reported as means and standard deviations or as medians and interquartile ranges (see Table 1). Pearson product-moment correlation analyses were performed to determine the association between Stroop performance variables and subjective ratings relative to type of emotion regulation use (i.e., reappraisal, suppression) and continuous MetS score.

Next, several regression models were conducted examining the association of cognitive reappraisal use with each construct of MetS (i.e., presence/absence, number of criteria met, continuous MetS score). First, simple logistic regression model was used to test the relationship between cognitive reappraisal use and presence/absence of the MetS. In this model, age and gender were entered in the first step of the equation, followed by ERQ reappraisal scores. The last step entered ERQ suppression scores to examine whether the effects of emotion regulation on the presence of MetS was specific to self-reported cognitive reappraisal use. Follow-up analyses were then performed by regressing the presence/absence of the individual components of the MetS (i.e., low HDL cholesterol or elevated blood pressure, plasma glucose, triglycerides, or waist circumference) on ERQ reappraisal scores adjusting for age, sex, and ERQ suppression score, similar to the logistic regression model described above. To aid interpretation and clearly

convey effect sizes, positive logistic regression coefficients are presented alongside odds ratios (OR; the exponentiated regression coefficient, e^B), and negative logistic regression coefficients alongside inverse odds ratios (IOR; the inverse of the exponentiated regression coefficient, $1/e^B$). Second, negative binomial models were conducted to examine the association between cognitive reappraisal use and number of MetS criteria met across the full sample of 139 participants. For these models, the number of MetS criteria met (ranging from 0-5) was regressed on age, gender, and ERQ reappraisal and suppression scores together in one model. These negative binomial results are presented alongside the exponentiated regression coefficients, and these can be interpreted as the change in number of criteria met per unit change in predictor of interest. Finally, ordinary least squares regression models were conducted to test whether cognitive reappraisal use covaried with continuous MetS scores. In this model, age and gender were entered in the first step of the equation, ERQ reappraisal scores in step 2, followed by ERQ suppression scores in the third, final step. All data were analyzed with Statistical Package for the Social Sciences (SPSS) version 20.0.

2.4.2 MRI Data Acquisition

All participants were scanned within a 3Tesla Trio TIM whole-body MRI scanner (Siemens, Erlangen, Germany), equipped with a 12-channel phased-array head coil to acquire data from the entire brain. Whole-brain fMRI data were acquired while participants completed the Stroop task within the scanner. To acquire the blood-oxygen level-dependent (BOLD) images from these functional scans, the following parameters were applied to a gradient-echo EPI sequence: field-of-view (FOV) = 205 x 206 mm^2, matrix size = 64 x 64 mm^2, time-to-repetition (TR) = 2,000 ms, time-to-echo (TE) = 28 ms, and flip angle (FA) = 90º. Thirty-nine slices (3-mm thick, no

gap) were obtained in an interleaved sequence in an inferior-to-superior direction, yielding 280 BOLD images (three initial discarded images, allowing for magnetic equilibration). We also obtained structural scans in order to facilitate with the spatial coregistration of the BOLD images. These T_1-weighted 3D magnetization-prepared rapid gradient echo (MPRAGE) neuroanatomical images were acquired over 7 min 17 s by these parameters: FOV = 256 × 208 mm^2, matrix size = 256 × 208 mm^2, TR = 2,100 ms BOLD images were acquired over the task period with a gradient-echo EPI sequence by these parameters ms, time-to-inversion (TI) = 1,100 ms, TE = 3.29 ms, and FA = 8° (192 slices, 1-mm thick, no gap).

2.4.3 fMRI Data Preprocessing

Neuroimaging data were preprocessed and analyzed using Stiatistical Parametric Mapping (SPM8; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm). The preprocessing steps included *(i)* image realignment; *(ii)* coregistration; *(iii)* normalization; and *(iv)* smoothing. Specifically, prior to basic fMRI analyses, BOLD images were spatially realigned to the first image in the run using a six-parameter rigid-body transformation. Realignment was performed to correct for head movements. These realigned images were then coregistered to each participant's T_1-weighted structural image. After the coregistration step, the images were then normalized by a 12-parameter affine transformation to the International Consortium for Brain Mapping 152 template (Montreal Neurological Institute; MNI). Lastly, spatial smoothing was applied to these normalized images with a 6-mm full-width-at-half-maximum (FWHM) Gaussian kernel.

After preprocessing, planned individual contrast maps were generated at fixed-effects level for each participant to investigate neural activity separately during the incongruent and

congruent conditions compared to baseline (fixation crosshairs) and to each other. These estimated contrast images corresponded to *(i)* "incongruent vs. congruent", *(ii)* "incongruent vs. fixation", and *(iii)* "congruent vs. fixation". However, much of the analyses in this project focused on the "incongruent vs. congruent" contrast maps as they presumably capture the interference effects of conflict manipulation tasks, including the Stroop paradigm, where task-relevant and task-irrelevant stimulus features are in conflict with each other (e.g.,(Bradley & Lang, 1994). Together, these contrasts permitted a determination of whether activation differences as a function of individual differences in use of reappraisal generalized across varying task conditions or were specific to activation patterns differentially elicited by incongruent versus congruent conditions ("incongruent > congruent" BOLD signal change). To this end, the incongruent, congruent, and fixation task conditions were modeled with rectangular waveforms that were convolved with the default SPM8 hemodynamic response function (HRF). For each participant, condition effects for each individual contrast image were estimated using the general linear model (GLM). These individual contrast maps were then utilized in further random effects whole brain and region-of-interest (ROI) group-level analyses across all participants. Of note, head movement parameters (3 translations, 3 rotations) derived from the realignment preprocessing step were included in these GLMs as regression vectors to account for BOLD signal changes due to head motion. Also, before GLM estimation, a 187-s temporal high-pass filter was applied to the data to account for low-frequency BOLD signal artifacts.

2.4.4 Basic fMRI Analysis

2.4.4.1 Main Effect Analysis

To examine neural activity reflecting Stroop color-word interference, region-of-interest (ROI) and whole-brain group-level analyses were performed that compared BOLD response during the incongruent condition relative to the congruent condition (i.e., "incongruent > congruent"). Hence, these initial main effect analyses both at the whole-brain and ROI level were conducted on these contrast images for each individual to confirm that the Stroop color-word interference task reliably engaged specific cognitive control brain regions (e.g., dACC, DLPFC) of interest.. First, based on a-priori predictions regarding the involvement of prefrontal and cingulate systems in implementing reappraisal and cognitive control, ROI analyses were performed to examine the effects of the incongruent Stroop condition on specific brain regions that jointly *(i)* monitor and initiate the demand for attentional control during response conflict (Bush et al., 2000; Kerns et al., 2004; MacDonald et al., 2000; Mohanty et al., 2007; Ridderinkhof et al., 2004), and *(ii)* select and apply cognitive reappraisal strategies to reduce negative affect (Kalisch, 2009; Ochsner & Gross, 2005; Phillips et al., 2008; Quirk & Beer, 2006). With respect to these existing reviews, these *a-priori* cognitive control ROIs were limited to Broadmann areas (BA) 9, 10, 24 and 32 in the medial PFC, and BA 8, 9, 10, 44, 45, 46, and 47 in the dorsal and ventral portions of the lateral PFC (see Section 2.4.4.2. on Region of Interest Analyses). Next, whole-brain analyses were performed to fully explore the neural regions beyond the above prefrontal cortical regions that are related to differential activity during the incongruent Stroop condition (vs. congruent condition) across each voxel in the brain. Additional ROI and whole-brain analyses were conducted on the contrast images reflecting brain activation related to "incongruent > fixation" to account for the incongruent color-word properties among three of the four response

choices during the *congruent* trials (see Figure 2). These alternate word choices serve as competitive response stimuli because they are part of the same color set as the correct answer choice, which may divert attention towards this stimulus dimension (i.e., color). Moreover, the congruent trials present another level of conflict by introducing task-irrelevant stimulus properties in word stimuli choices that is not consistent with the ink color (e.g., the word RED and GREEN are printed in red ink). Hence, it is important to consider the BOLD signal changes that reflect "incongruent > fixation" since this comparison condition ("fixation") is not confounded by the slightly conflictual aspects of the congruent condition. All ROI and whole-brain analyses were thresholded at $p < 0.005$ with a 20-voxel cluster (k) extent threshold. All brain coordinates are reported in Montreal Neurological Institute (MNI) format.

2.4.4.2 Region of Interest Analyses

Given our a-priori hypotheses regarding the relationship between cognitive reappraisal, autonomic physiology relevant to the MetS, and prefrontal cortical regions, several ROI analyses focusing on various prefrontal and cingulate regions were performed. The dACC (BA 24/32) ROIs were anatomically defined according to a four-region model of the cingulate cortex (Yu et al., 2011). From this model, ROI 4 was used for our dACC ROI (see Figure 1 in Yu et al., 2011) due to its positive connectivity with the fronto-parietal cognitive control network that has previously been linked to individual differences in reappraisal use (Drabant et al., 2009). The dimensions for this dACC ROI had a center of mass of x = -2, y = 21, and z = 26. It extended along the x- y- and z- directions from a minimum (min) x-coordinate of 8 mm to a maximum (max) x-coordinate of -12 mm; a min y of 34 mm to a max y of 8 mm; a min z of 36 mm to a max z of 15 mm. It had a volume of 3294 mm^3. The anatomic boundaries for the other ROIs within the medial, lateral, and ventral PFC regions (i.e., BA 8, 9, 10, 44, 45, 46, 47) were defined

using the respective Broadmann areas from the Talairach Daemon database within WFU_PickAtlas toolbox (Lancaster et al., 2000; Maldjian, Laurienti, Kraft, & Burdette, 2003; http://fmri.wfubmc.edu/software/PickAtlas).

These prefrontal and cingulate ROIs were used to address two questions. First, we examined the main effect of neural activity within each prefrontal and cingulate ROI during the incongruent *vs.* congruent contrast. Next, we examined whether activity in these ROIs correlated with ERQ reappraisal scores and the MetS. To examine this, mean parameter estimates for each participant were extracted from the ROIs during the "incongruent > congruent" contrast image. These parameter estimates within these ROIs were determined by the eigenvariate option wherein the first eigenvariate value was extracted from 3D spheres of 5-mm radius centered on the voxel of maximum activity within the ROIs for each participant. These parameter estimates were submitted to SPSS for further correlational and regression analyses.

To examine whether cognitive reappraisal use was associated with increased BOLD response within these cognitive control ROIs, correlational analyses were run that related ERQ reappraisal scores to ROI parameter estimates. Follow-up partial correlation analyses examined whether the association persisted after controlling for age, sex, and ERQ suppression scores.

We conducted various regression models to examine whether the MetS (i.e., presence/absence, number of criteria met, continuous MetS score) was associated with decreased neural activity within these prefrontal cognitive control ROIs. These regression models are similar to those reported in Section 2.4.1. The association between presence of the MetS and neural activity within each ROI was determined through simple logistic regression models adjusting for age and gender in Step 1, followed by neural activity in each of these *a-priori* ROIs. The association between number of syndrome criteria met and neural activity in each ROI

was tested with negative binomial models. Hence, separate binomial models were run for each ROI, such that the number of MetS criteria met (ranging from 0-5) was regressed on age, gender, and neural activity within a specific prefrontal cortical ROI. Lastly, correlational analyses were used to test whether neural activity in each ROI was associated with continuous MetS scores. Follow-up partial correlation analyses examined whether the association persisted after controlling for age, sex. For all these analyses, a Bonferroni-corrected α-level of 0.004 was used as the criterion of statistical significance in order to account for multiple comparisons and maintain the 5% Type I error rate.

2.4.4.3 Whole Brain Analyses

Additional whole-brain analyses were performed to supplement the ROI analyses and to completely explore the neural regions during incongruent conditions relative to the congruent condition across the entire brain. Next, we performed whole-brain regression analyses within SPM8 examining the correlations between neural activity during the incongruent *vs.* congruent conditions and self-reported reappraisal and suppression use. Age and gender were added to these models to account for the age- and gender-related differential activity in prefrontal cortical brain regions during cognitive reappraisal (McRae, Jacobs, Ray, John, & Gross, 2012; Opitz, Rauch, Terry, & Urry, 2012). To determine the specificity of reappraisal use in predicting neural activity, additional whole-brain regression models were run controlling for another common form of emotion regulation, namely suppression use, alongside age and gender.

2.4.4.4 Psychophysiological Interactions

With respect to our exploratory hypotheses, we performed a psychophysiological interaction analysis (PPI; Friston et al., 1997) to identify prefrontal cortical regions (i.e., DLPFC) exhibiting

an increase in correlation with the dACC BOLD signal activity during the incongruent condition. In extension, an added goal was to test whether cognitive reappraisal use and the MetS was related to the incongruent-specific temporal covariation between dACC and DLPFC regions that might be functionally implicated in mediating cognitive control processes underlying conflict resolution (Mohanty et al., 2007) as well as emotion regulation (Ochsner, Silvers, & Buhle, 2012). For these PPI analyses, the dACC ROI was selected as our "seed" region (see Section 2.4.4.2. on Region of Interest Analyses) for several reasons. Most conflict models of cognitive control emphasize a unidirectional flow of informational between prefrontal cognitive control networks, with the dACC exhibiting a broad role in modulating the need for cognitive control from DLPFC regions that resolve response conflict (Badre & Wagner, 2004; Sallet et al., 2011). Consistent with this, MacDonald et al. (2000) found that the dACC was more active during incongruent trials of the Stroop while DLPFC was more active during the act of selecting the color name, which together converges with the presumptive conflict monitoring roles of the dACC in monitoring for conflictual, incongruent stimuli and the DLPFC in maintaining representations of task goals through behavior adjustments. Further, Nee, Wager, & Jonides (2007) indicated that increased conflict-related ACC activity characterized the incongruent *vs.* congruent contrasts to greater extent than the greater DLPFC activity that appears to be exhibited during incongruent *vs.* fixation/neutral contrasts. Hence, since the exploratory hypotheses were based on conflict models of cognitive control, identifying the dACC as a "seed" region for this cognitive control neural network agreed with theoretical and experimental evidence that the dACC informs subsequent activity in DLPFC depending on psychological context.

Towards that end, we employed PPI analyses that utilized multiple regression models to isolate the brain regions exhibiting functional coupling with the dACC ROI as a function of

experimental design or task manipulation ("incongruent > congruent"). For PPI analyses, the functional coupling between the various brain regions serves as the *physical component* while the different task conditions define the *psychological component*. These two components characterize two of the three vectors within the PPI design matrix. The third vector is an interaction term of the physical and psychological vectors that provides a PPI measure or rather a correlation in neural activity between the dACC "seed" region and the functionally coupled brain regions that differ between "incongruent *vs.* congruent" conditions. Thus, significant PPI measures indicate that coactivation between the dACC "seed" region and different brain regions were significantly greater during incongruent conditions of the Stroop task than congruent conditions.

To perform the PPI analyses, individual time-series were extracted for each participant from the BOLD signal activity in all voxels within a 5 mm radius sphere around the peak activation voxel of dACC ROI mask. Next, this dACC BOLD signal time-series was mean-centered and submitted to a deconvolution algorithm using the canonical SPM8 HRF. Following deconvolution, the PPI vector was defined as the interaction term of the deconvolved dACC ROI time-series and a vector coding for the two main effects of the Stroop task (incongruent, congruent). This time-series by task condition interaction vector was re-convolved with the SPM8 HRF to create the final PPI vector. To examine the effect of this PPI task-by-seed interaction term, activity within the dACC ROI mask was regressed on a voxel-wise basis against this interaction term. This resulted in estimated individual PPI contrast images that were entered into second-level random effects analysis in which task-dependent effects ("incongruent > congruent") were tested using one-sample *t*-tests. These random effects analyses on the individual PPI maps identified any brain areas that exhibited activity that covaried with that of

the dACC significantly more during the incongruent than congruent task, and vice versa. Significant clusters exhibiting PPI-related dACC coupling were identified with a voxel-wide threshold of $p < 0.005$ with a 20-voxel extent threshold.

Additional regression models as describe in Section 2.4.1. were used to test whether a measure of task-dependent functional connectivity between dACC-DLPFC was associated with ERQ reappraisal scores and the three measures of the MetS. An extracted PPI beta estimate reflecting the coupling between the dACC and DLPFC ROI was used in these analyses.

2.4.4.5 Exploratory Mediation Analyses

For each of the prefrontal and cingulate ROIs that were significantly related to habitual cognitive reappraisal use and/or MetS, we performed an exploratory mediation analyses to test whether cognitive control-related neural activity within these ROIs might partially explain the link between individual differences in reappraisal use and the MetS. Based on our results (see Section 3.4 in Results), none of the individual prefrontal and cingulate ROIs met criteria for a test of mediation. Instead, the dACC-DLPFC functional connectivity values were submitted to mediation analyses to test for the indirect effect of cognitive reappraisal on the MetS through this cortico-cortical functional pathway between the dACC and the DLPFC. More precisely, we used the product-of-coefficients strategy that tests the significance of the indirect effect (i.e., the path through the mediator) by bootstrapping the product of the effect of the independent variable on the mediator (path *a*), and the effect of the mediator on the dependent variable accounting for the effect of the independent variable (path *b*). However, the sampling distribution of the indirect effect that is determined through the *ab* product of coefficients is subject to violations of normality when the possibility of mediation is present (Shrout & Bolger, 2002). Hence, Preacher

& Hayes (2008) recommend using a bootstrapping approach whereby 5000 estimates of *ab* are used to calculate confidence intervals (CIs) and standard errors around the indirect effect.

In these mediation analyses, ERQ reappraisal scores served as the independent variable, presence of the MetS, the number of MetS criteria met, or continuous MetS score served as the dependent variable, dACC-DLPFC PPI estimates served as the mediator, and age, gender, and ERQ suppression scores were included as covariates. These mediation analyses were scripted within SPSS 20.0 using the INDIRECT macro (Preacher & Hayes, 2008).

3.0 RESULTS

3.1 DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Demographic characteristics of the sample are displayed in Table 1. As expected, participants that met criteria for the MetS exhibited significantly poorer outcomes on all components of the syndrome. Individuals with the MetS also showed increased high sensitivity C-reactive protein (CRP) levels.

Although there was no gender difference in the prevalence of the MetS in this sample, χ^2 (1, 139) = 0.02, p = 0.89, there were gender differences in the syndrome components. Specifically, the means of waist circumference, fasting glucose and triglyceride levels, and systolic and diastolic BP were higher in men relative to women, ts < 2.54, ps < 0.02. In addition, men had lower levels of HDL-cholesterol than women, t = -4.70, p < 0.00001. Further, men had a higher continuous MetS score than women, t (137) = -4.66, p < 0.00001; men: M = 1.22, SD = 2.84; women: M = 1.39, SD = 3.77. Low HDL-cholesterol was the most frequent component in men (45.9%) followed by high BP (29.7%), high waist circumference (20.3%), high triglycerides (17.6%), and high fasting glucose (10.8%). For women, high waist circumference (44.6%) was the most frequent component followed by low HDL-cholesterol (38.5), high BP (20%), high fasting glucose (9.2%), and high triglycerides (6.2%).

For everyday use of emotion regulation strategies, men made less habitual use of reappraisal compared to women, t (137) = -2.77, p = 0.006; men: M = 30.42, SD = 5.64; women: M = 33.06, SD = 5.59. In contrast, men reported greater habitual use of suppression relative to women, t (137) = -2.96, p = 0.004; men: M = 14.54, SD = 4.71; women: M = 12.34, SD = 3.98. This finding is consistent with reports that women tend to utilize suppression less as an emotion regulatory strategy than men (Gross & John, 2003). Age was positively associated with habitual use of suppression, r = 0.19, p = 0.03, although no relationship was found with reappraisal use.

3.2 BEHAVIORAL PERFORMANCE AND RATINGS

3.2.1 Behavioral Performance and Affective Responses to Stroop Task

There were significant differences in reaction time and accuracy between the incongruent and congruent trials of the Stroop task (see Table 1). Consistent with the conflict-monitoring hypothesis (Botvinick et al., 2004), during the fMRI testing session, incongruent trials were associated with a longer reaction/response time (RT) relative to congruent trials, t (138) = 32.53, p < 0.01; incongruent: M = 1811.70 ms, SD = 420.19 ms; congruent: M = 1278.94 ms, SD = 274.89 ms.

The Stroop task relative to the baseline period led to a significant increase in self-reported ratings of arousal, t (137) = -16.43, ps < 0.01, and decreased ratings of perceived control and positive valence, ts (137) > 9.94, ps < 0.01. This confirms that the Stroop task was subjectively distressing. Interestingly, there was a gender difference in the change in self-reported control, with women reporting a greater loss of control following the completion of the Stroop task

(relative to baseline) compared to men, t (136) = 2.53, ps < 0.05; men: M = -1.53, SD = 2.27; women: M = -2.54; SD = 2.39. Thus, along with the conflictual nature of the incongruent Stroop condition, individuals also reported that the Stroop task was largely arousing, distressing, and marked by a loss of control.

Taken together, the behavioral responses and the subjective ratings elicited by the Stroop task indicate that the incongruent condition produced an interference effect and a concomitant unpleasant emotional state that was characterized by increased arousal and decreased valence and perceived control. It is interesting to note that the behavioral demands of the incongruent condition (i.e., as reflected by the Stroop RT interference effect) did not covary with self-reported changes in any of the subjective ratings (ps > 0.25). Hence, the Stroop task appears to evoke a state of subjective distress that is apparently dissociable from or independent of observable behavioral performance on the task itself. Thus, in the face of the same task and behavioral demands, individuals differ significantly in the extent to which they report changes in affect, arousal, and control. Put differently, it does not appear that worse performance necessarily evokes more distress across subjects.

3.2.2 Emotion Regulation and Behavioral and Affective Responses to Stroop Task

Next tested was whether individual differences in the typical use of reappraisal or expressive suppression associate with task performance and subjective ratings during the Stroop task. Accuracy did not exhibit any significant associations with everyday use of reappraisal or expressive suppression (i.e., percentage of correct trials in the incongruent and congruent Stroop conditions did not covary with reappraisal or suppression, ps > 0.61). The RT data appeared to

converge with these findings, with reappraisal and expressive suppression showing no significant correlations with RT (all *ps* > 0.05).

No associations were found between habitual use of reappraisal and change in perceived control or arousal following the Stroop task after adjusting for age, gender, and baseline ratings for the respective subjective scores (*ps* > 0.22). Although there were outliers (scores > 3 SDs from the mean) in the subjective change scores for the arousal (n = 1) and control (n = 1) distributions, these results remained nonsignificant even after removal of these individuals' data. However, everyday reappraisal use was positively associated with self-reported change in valence following the Stroop task after controlling for age, sex, and baseline valence ratings, $r_{partial}$ = 0.17, p = 0.046. Of note, use of expressive suppression in everyday life was not associated with any of the subjective rating measures (*ps* > 0.53).

3.2.3 Effect of the Metabolic Syndrome on Behavioral and Affective Responses to Stroop Task

Additional analyses also examined whether the MetS related to Stroop performance and task-related changes in self-reported ratings on arousal, valence, and control. Presence or absence of the MetS did not covary with Stroop performance (i.e., RT, accuracy rates; all *ps* > 0.62). Similarly, number of MetS criteria met or the continuous MetS score demonstrated no association with on the two Stroop performance measures (all *ps* > 0.05).

ANCOVAs revealed no significant between-group differences for the MetS on change in arousal, valence, or perceived control after adjustments age, gender, and the respective baseline rating for each subjective scale (all *ps* > 0.19). It is interesting to note that there was a trend for individuals with the MetS to report greater loss of perceived control following the Stroop task as

compared to those not meeting MetS criteria, F (1, 132) = 1.80, p = 0.18, after adjustment for age, sex, and baseline control rating. Hence, although individuals with the MetS experienced increases in arousal and distress coupled with reduced control during the Stroop task relative to baseline (see Table 1), these differences were not significant. Neither number of syndrome criteria met nor the continuous MetS score were associated with any change scores in subjective ratings (all *ps* > 0.23).

3.3 EMOTION REGULATION AND THE METABOLIC SYNDROME

First, to replicate previous reports (Kinnunen et al., 2005), we tested for the associations between cognitive reappraisal use and the various constructs of MetS. As expected, individuals who exhibited a tendency to use cognitive reappraisal were less likely to have the MetS after adjusting for age and sex, β = -0.72, SE = 0.25, OR = 0.485, IOR = 2.06, p = 0.004. Here, a decrease of one standard deviation in everyday use of cognitive reappraisal was associated with a 2.06 times increased odds of meeting criteria for the MetS. More importantly, this relationship between habitual reappraisal use and presence of the MetS remained significant even when accounting for suppression use (p = 0.003). Similar results were observed with number of MetS criteria met. Specifically, negative binomial models revealed that habitual reappraisal use was inversely associated with number of syndrome components met, β = -0.16, SE = 0.08, e^B = 0.85, p = 0.039, above and beyond age, sex, and expressive suppressive use. Lastly, the tendency to use cognitive reappraisal negatively covaried with continuous MetS score, β = -0.18, t = - 2.24, p = 0.027, after controlling for demographic covariates and suppression use (Figure 5). Combined, everyday reappraisal use is associated with a reduced likelihood of meeting criteria for the MetS,

meeting fewer MetS criteria, and having a lower cardiometabolic risk profile above-and-beyond demographic factors and other common forms of emotion regulation (i.e., expressive suppression) related to cardiovascular health (Mauss & Gross, 2002).

Among the syndrome components, individual differences in reappraisal use were inversely associated with meeting criteria for elevated triglycerides, β = -0.68, *SE* = 0.28, *IOR* = 1.96, p = 0.015, and elevated waist circumference, β = -0.48, *SE* = 0.20, *IOR* = 1.61, p = 0.019, after adjusting for demographic factors and suppression use. Conversely, although suppression use was not associated with the MetS, there was evidence of a positive trend between the tendency to suppress emotional behavior and meeting criteria for reduced HDL-cholesterol, β = 0.33, *SE* = 0.19, *IOR* = 0.72, p = 0.087, net the influence of age, sex, and reappraisal use. Hence, it seems that individual differences in use of emotion regulation strategies are associated with presence of specific syndrome components.

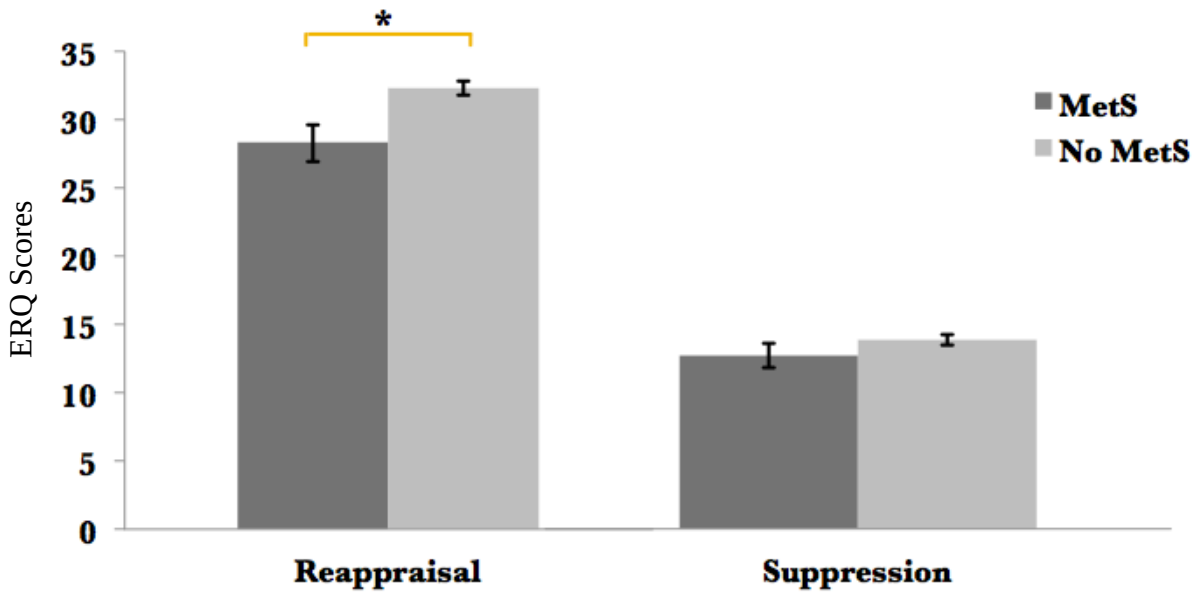

Figure 3. Main effect of MetS group on ERQ reappraisal and suppression scores.

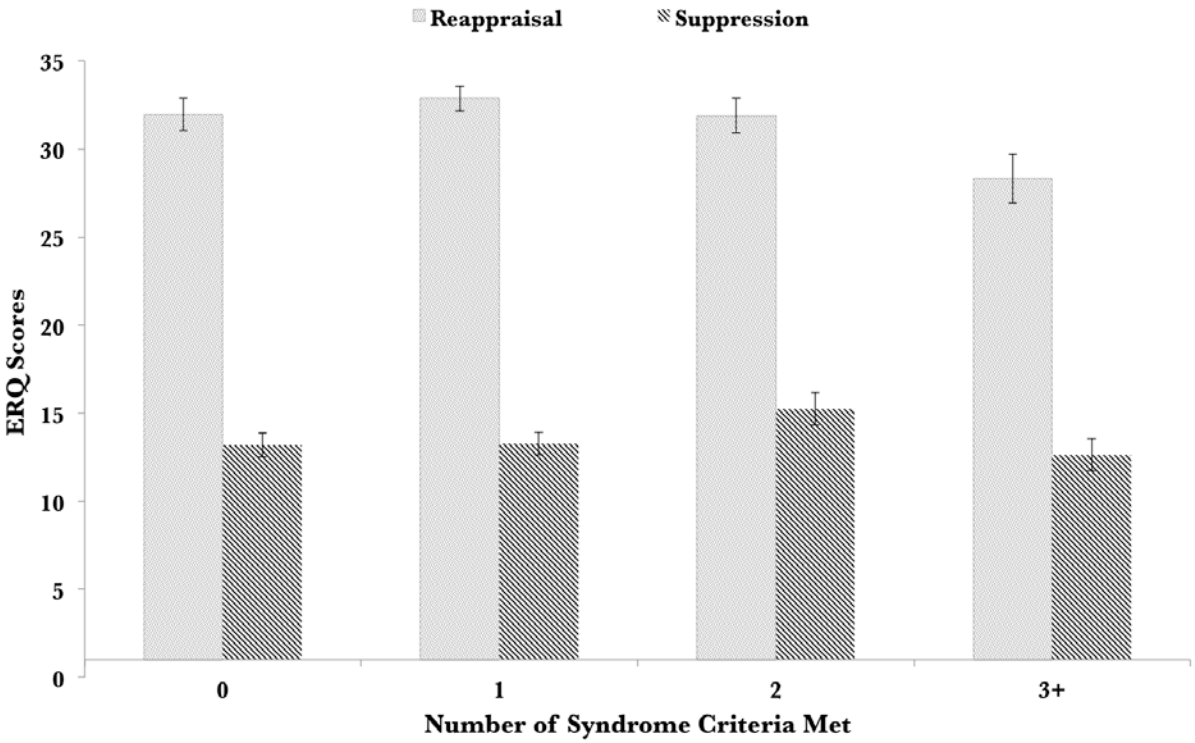

Figure 4. Relationship between number of metabolic syndrome criteria met and ERQ reappraisal and suppression scores.

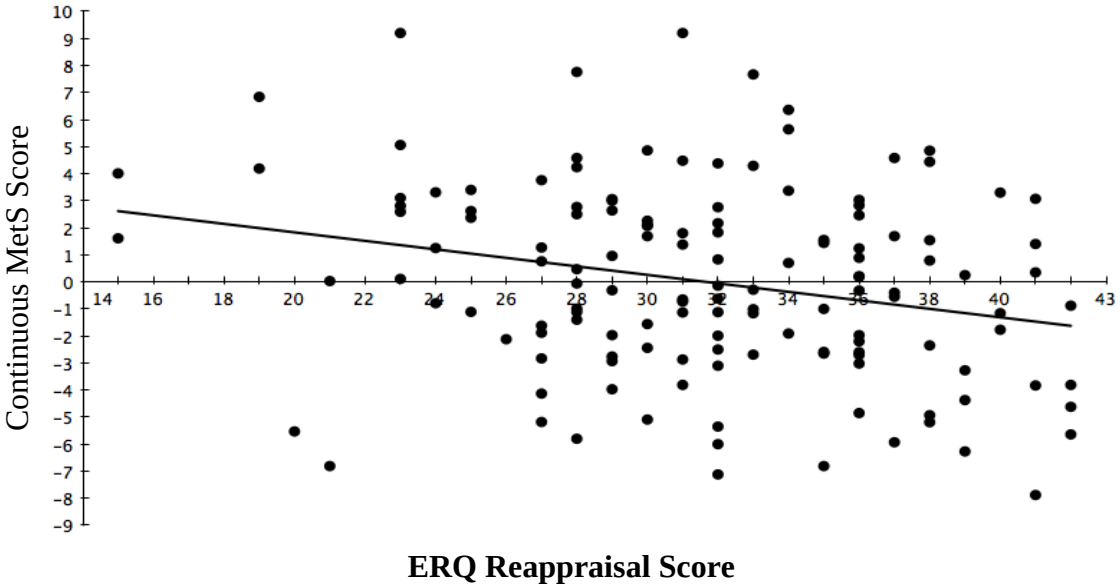

Figure 5. Scatterplot illustrating the inverse relationship between ERQ reappraisal scores and continuous MetS score.

3.4 FMRI RESULTS

3.4.1 Neural Correlates of Stroop Color-Wood Interference Task

ROI and whole-brain main effect analyses were performed on the Stroop task to determine which brain regions showed an enhanced BOLD response during incongruent compared with congruent task conditions. Consistent with prior work, brain activity within the control-related prefrontal and cingulate ROIs was significantly greater during the "incongruent > congruent" contrast. Similarly, whole-brain analyses indicated that the incongruent condition produced greater activation in prefrontal and cingulate areas previously identified in studies of cognitive control of emotion through reappraisal (Kalisch, 2009; Ochsner & Gross, 2008; Ochsner et al., 2012; Phillips et al., 2008), including mPFC/dACC (BA 32), DLPFC (BA 9/46), (BA 47), and lateral OFC (BA 10; see Figure 6A, 6B, and Table 2). We did observe a brain-behavior relationship between left VLPFC activity and Stroop RT interference effect (r = 0.24, p = 0.004), which is consistent with a presumed functional role of the left inferior frontal gyrus as an executive control mechanism engaged by conflictual working memory tasks that involve language processing (e.g., Nelson, Reuter-Lorenz, Persson, Sylvester, & Jonides, 2009). In addition to engaging these prefrontal cognitive control areas, the incongruent condition of the Stroop task activated other brain regions that likely support behavioral performance in the context of task-related cognitive and autonomic physiological changes, including insula, cerebellum,

supplementary motor area (BA 6), and superior temporal (BA 22) and parietal lobule (BA 7; Fechir et al., 2010; Gianaros, Onyewuenyi, Sheu, Christie, & Critchley, 2012).

3.4.2 Neural Correlates of Emotion Regulation

The next set of analyses examined whether self-reported use of emotion regulation strategies covaried with functionally-defined, prefrontal and cingulate ROIs (i.e., dACC, DLPFC, VLPFC, lateral OFC) identified during the incongruent condition of the modified Stroop task.

Contrary to our hypotheses and other reports (Drabant et al., 2009; Vanderhasselt et al., 2012) self-reported reappraisal use did not demonstrate any significant positive or negative associations with BOLD response restricted to *a priori* ROIs within the dACC, DLPFC, VLPFC, lateral OFC, $-0.001 < rs < -0.059$, $ps > 0.10$. These findings remained in subsequent hierarchical regression analyses including age and sex as covariates. Similarly, suppression use was not associated with BOLD response in these prefrontal and cingulate ROIs. Additional whole-brain regressions analyses within SPM replicated the null findings demonstrated with the ROIs.

3.4.3 Neural Correlates of the Metabolic Syndrome

Next, the effect of the MetS (i.e., presence or absence, number of criteria, and cMetS score) on BOLD activation values in these *a priori* ROIs was also examined. However, inconsistent with some previous studies (Hoth et al., 2011), we failed to find an association between any of the three MetS construct measures and BOLD response signal changes within our prefrontal and cingulated ROIs, even when less conservative statistical thresholds were used ($ps > 0.10$).

Additional whole-brain regressions analyses within SPM replicated the null findings demonstrated with the ROIs.

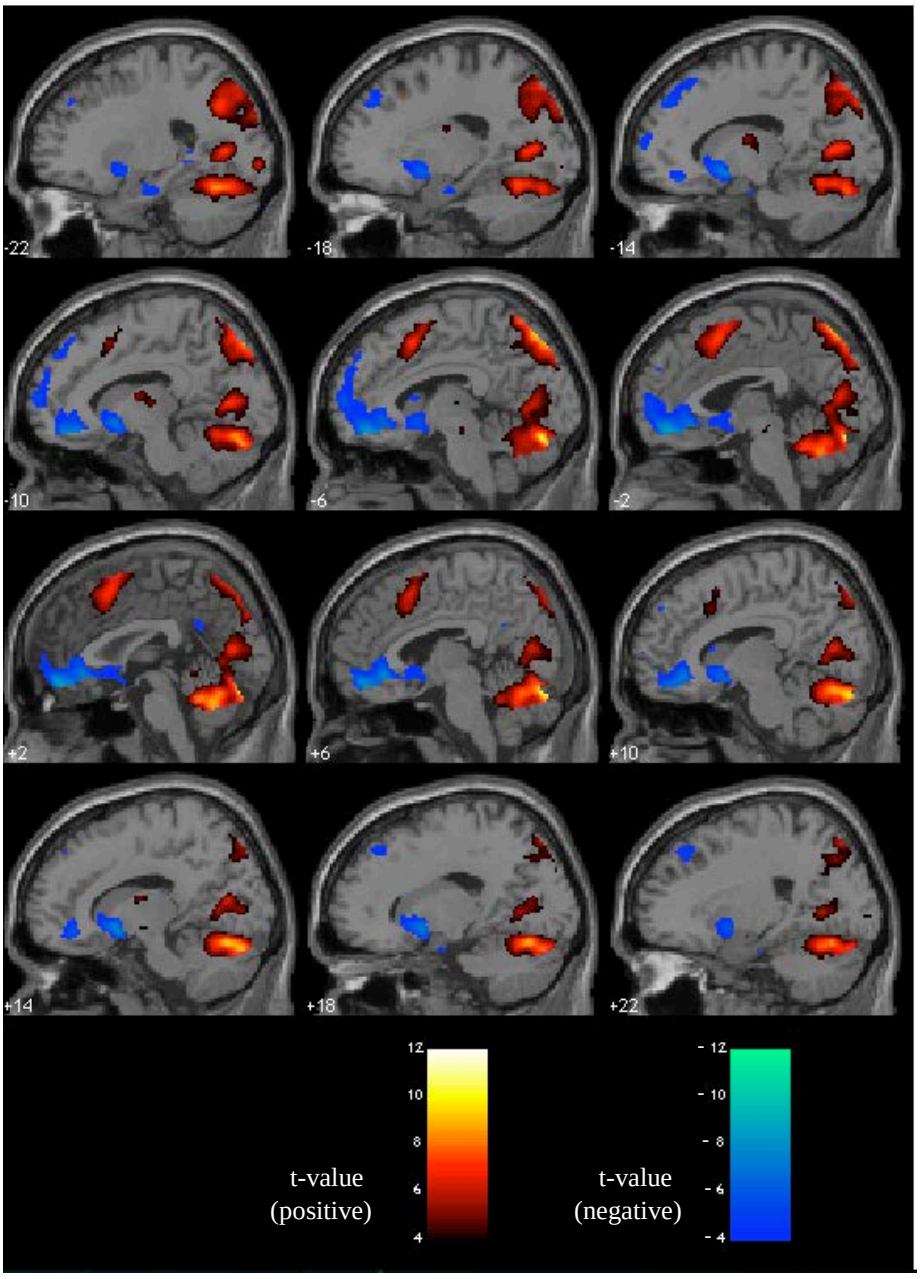

Figure 6. Main effects of the Stroop color-word interference task: incongruent > congruent. Statistical parametric maps showing sagittal view of dACC (BA 32) activations extending into supplementary motor areas. *T*-values are represented by the intensity of the activation.

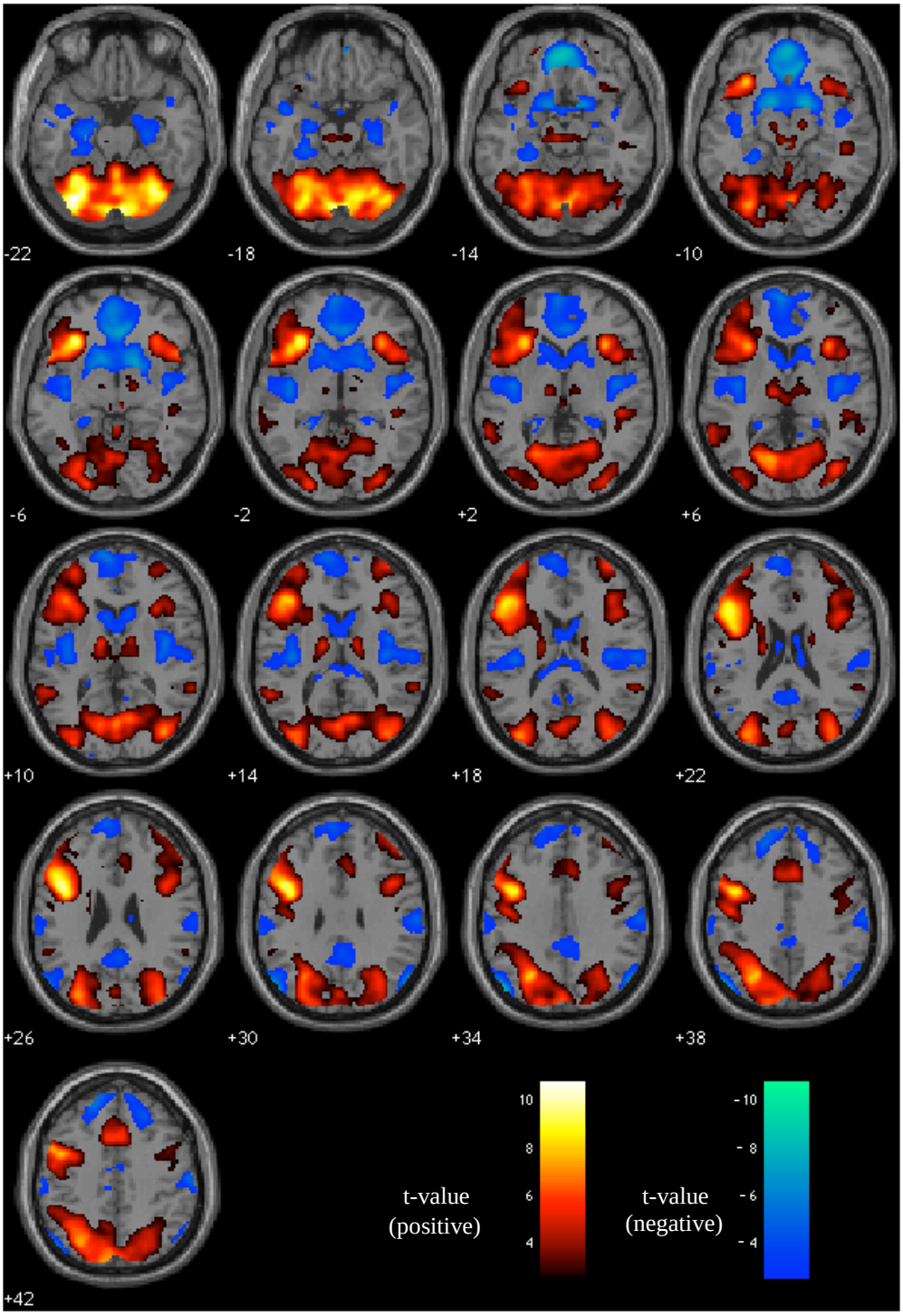

Figure 7. Main effects of the Stroop color-word interference task: incongruent > congruent. Statistical parametric maps showing axial view of DLPFC and VLPFC activations as well as insular regions. *T*-values are represented by the intensity of the activation.

Table 2. Brain areas showing significantly increased BOLD activity for the 'Incongruent > Congruent' condition contrast in random effects model (see Figures 6 and 7)

Side	Region	BA	MNI coordinates (peak)			t-value	voxels
			x	y	z		
L	Cerebellum, fusiform gyrus	19	-34	-72	-22	10.86	21379
R	Cerebellum		34	-66	-36	10.35	
R	Cerebellum, lingual gyrus		6	-80	-22	10.29	
L	Inferior frontal gyrus, insula	47	-32	26	-4	10.14	8158
L	Inferior/middle frontal gyrus	9/46	-42	8	28	10.13	
L	Inferior/middle frontal gyrus	46	-46	24	20	9.24	
R	Insula, inferior frontal gyrus	45/47	34	24	2	7.64	3765
R	Inferior frontal gyrus (VLPFC), superior temporal gyrus	47/38	50	16	-6	6.50	
R	Inferior frontal gyrus (DLPFC)	9	42	10	28	5.75	
L/R	Dorsal anterior cingulate cortex, medial frontal gyrus, supplementary motor area	32/6	-4	14	50	7.43	1835
L/R	Supplementary motor area, superior frontal gyrus		0	10	62	6.96	
L/R	Supplementary motor area	6	16	12	60	2.92	
R	Superior temporal gyrus	22	48	-32	2	4.91	469
R	Superior temporal gyrus	13	60	-44	12	4.39	
R	Sub-gyral		48	-30	-10	4.24	

Note. Next to each left (L) and right (R) region and approximate Brodmann area (BA) are the MNI coordinates (for the peak voxel in each cluster), where x = right (+) to left (-); y = anterior (+) to posterior (-); z = superior (+) to inferior (-). T-values for voxels of peak activation and their corresponding cluster extents were derived from a random-effects analysis employing a height threshold of $P < 0.005$ and extent cluster threshold of $k = 20$ voxels.

Table 3. Brain areas showing significantly increased BOLD activity for the 'Congruent > Incongruent' condition contrast in random effects model (see Figures 6 and 7)

Side	Region	BA	MNI coordinates (peak)			t-value	voxels
			x	y	z		
R	Perigenual anterior cingulate cortex	24/32	4	32	-10	7.48	
L	Inferior parietal lobule, middle temporal/angular gyrus	39	-48	-74	36	8.15	422
L	Supramarginal gyrus	40	-58	-58	36	3.36	
R	Angular/middle temporal gyrus, inferior parietal lobule	39	54	-68	34	6.54	265
R	Superior temporal gyrus	39	58	-64	24	4.35	
R	Angular gyrus		48	-68	44	4.22	
R	Postcentral/precentral gyrus		54	-20	54	6.26	2896
R	Precentral gyrus	6	60	-18	46	5.69	
R	Insula, superior temporal gyrus	13/22	40	-8	10	5.45	
L/R	Posterior cingulate, precuneus	31	4	-50	28	4.38	646
L	Posterior cingulate		-4	-52	22	3.82	
R	Cingulate gyrus		0	-40	34	3.75	
R	Parahippocampal gyrus, caudate		26	-40	2	3.85	93
L/R	Mid cingulate	24	2	-8	46	3.43	138
	Supplementary motor area	24	10	-6	50	2.69	

Note. Next to each left (L) and right (R) region and approximate Brodmann area (BA) are the MNI coordinates (for the peak voxel in each cluster), where x = right (+) to left (-); y = anterior (+) to posterior (-); z = superior (+) to inferior (-). T-values for voxels of peak activation and their corresponding cluster extents were derived from a random-effects analysis employing a height threshold of $P < 0.005$ and extent cluster threshold of $k = 20$ voxels.

Table 4. Brain areas showing significantly greater functional connectivity with dorsal anterior cingulate cortex seed during the performance of the 'Incongruent' condition of the Stroop task

Side	Region	BA	MNI coordinates (peak)			t-value	voxels
			x	y	z		
L	Dorsal anterior cingulate cortex	24/32	-12	22	26	7.00	30138
L/R	Medial frontal gyrus	9/10	6	50	16	6.99	
L	Superior/medial frontal gyrus	9/10	-14	46	18	6.85	
L	Superior temporal gyrus	22	-52	-18	0	4.21	307
L	Middle temporal gyrus	20	-56	-42	-8	3.91	
L	Superior temporal gyrus	21	-58	-24	-4	3.60	
R	Pre-central gyrus	4	16	-28	64	4.13	335
R	Medial frontal gyrus, supplementary motor area	6	8	-12	56	3.52	
R	Medial frontal gyrus, supplementary motor area		10	-22	60	3.38	
L	Supramarginal/angular gyrus		-46	-60	32	4.01	447
L	Inferior parietal lobule	40	-50	-56	46	3.99	
L	Inferior parietal lobule, angular gyrus	40	-42	-66	48	3.89	
L	Paracentral lobule	6/4	-14	-28	62	3.66	145
L	Paracentral lobule		-6	-38	64	3.18	
R	Hippocampus		28	-28	-6	3.63	28
L	Superior/middle temporal gyrus		-42	-42	6	3.60	51
L	Superior temporal gyrus		-34	-38	4	2.88	
L	Precuneus	31/7	-16	-50	38	3.58	40
R	Middle temporal gyrus	21	48	4	-26	3.58	63
R	Superior temporal gyrus	38	42	12	-26	3.50	
L	Posterior cingulate, precuneus		-6	-54	22	3.58	39
L	Thalamus		-6	-28	10	3.51	110
	Thalamus		0	-34	10	3.49	
R	Middle temporal gyrus	21	64	-42	-6	3.47	457
R	Middle temporal gyrus		50	-18	-6	3.43	
R	Middle temporal gyrus		56	-34	-8	3.42	
R	Hippocampus		26	-32	8	3.40	53
R	Precuneus		24	-46	10	3.15	
L	Insula	13	-32	-28	20	3.29	47
L/R	Subgenual anterior cingulate cortex	25	0	8	-6	3.17	25
L	Parahippocampus gyrus	19	-30	-48	-8	3.12	20
R	Pre-central gyrus	6	54	-6	8	3.09	25
R	Pre-central gyrus		48	-2	12	2.78	
			-24	-32	44	2.96	21

Note. Next to each left (L) and right (R) region and approximate Brodmann area (BA) are the MNI coordinates (for the peak voxel in each cluster), where x = right (+) to left (-); y = anterior (+) to posterior (-); z = superior (+) to inferior (-). T-values for voxels of peak connectivity and their corresponding cluster extents were derived from a random-effects analysis employing a height threshold of $P < 0.005$ and extent cluster threshold of $k = 20$ voxels (see Figures 8).

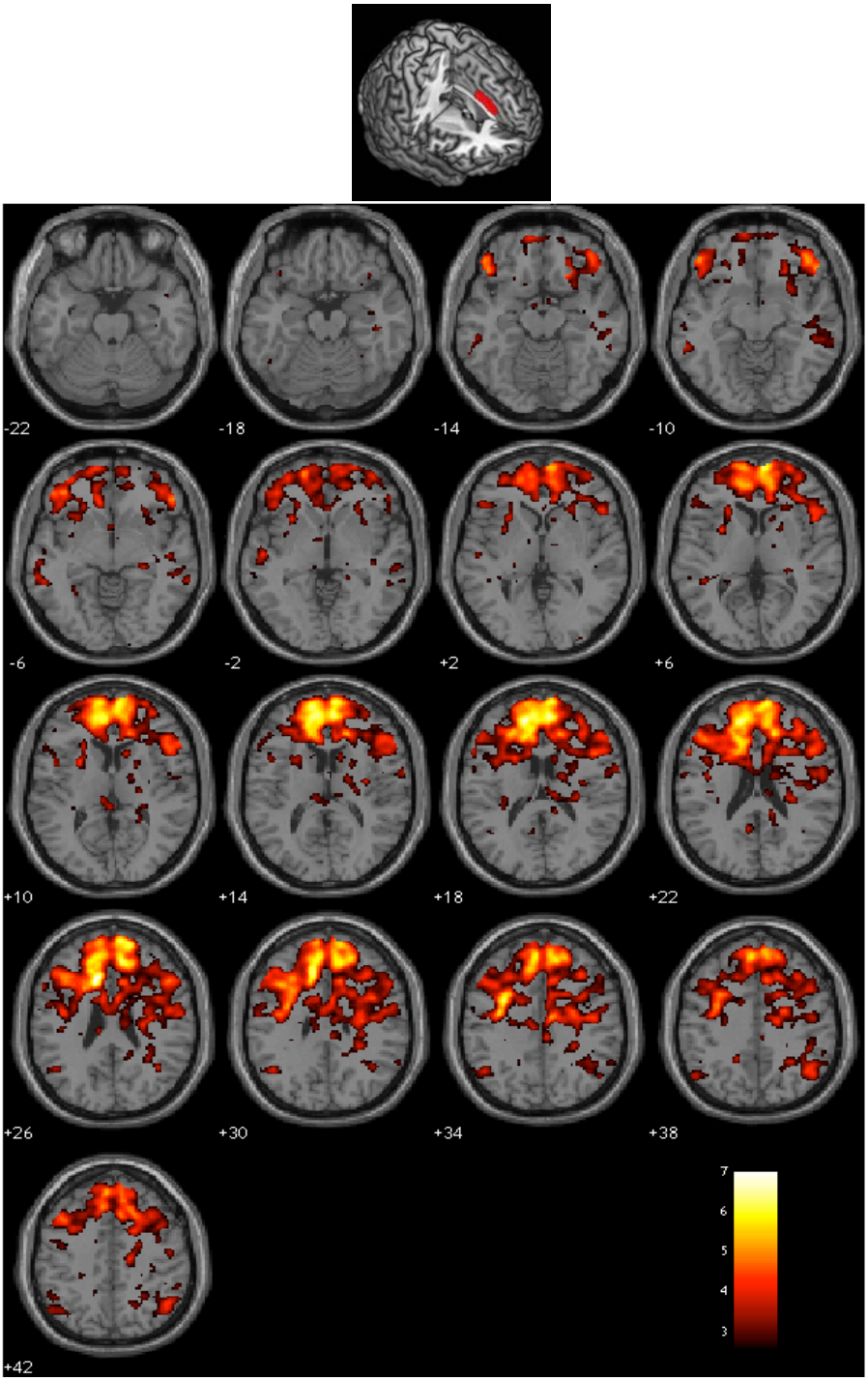

Figure 8. Functional connectivity map illustrating right DLPFC regions that evidenced positive correlated activity with the dACC seed region during the incongruent Stroop conditions.

3.4.4 Functional Interactions between dACC and DLPFC

The final step in the fMRI analyses examined whether the BOLD response signal changes during the "incongruent > congruent" contrast could be characterized by increased functional connectivity within an established cognitive control network, particularly between the dACC and DLPFC. We tested this hypothesis by conducting exploratory PPI analyses that were constrained to correlated neural activity in the dACC and DLPFC ROIs. Further, we explored whether temporally coupled BOLD signal changes in the dACC and DLPFC covaried with self-reported reappraisal and suppression use and as well as our various constructs of the MetS.

PPI analyses indicated that activity in the dACC "seed" exhibited task-related positive functional connectivity with the DLPFC (BA9/46). Additional whole-brain analyses confirmed that dACC activity was more strongly positively correlated with regions of the DLPFC during the incongruent trials than during the congruent trials (see Figure 8, Table 3).

3.4.4.1 Correlates of dACC and DLPFC Functional Connectivity

Next, we examined whether the task-dependent coupling of the dACC with the right DLPFC was associated with individual differences in typical emotion regulation use and the MetS. First, we found a positive relationship between cognitive reappraisal use and functional connectivity between the dACC and a cluster within the DLPFC ROI (*x*,*y*,*z* 52, 22, 26) during incongruent trials, net the influence of age and gender ($\beta = 0.21$, $t = 2.45$, $p = 0.016$). Moreover, this positive dACC-DLPFC connectivity was inversely associated with presence of the MetS, number of

syndrome criteria met, and the continuous MetS score after adjusting for age, gender, and suppression use ($ps < 0.006$).

We also observed a brain-behavior relationship between dACC-DLPFC connectivity and accuracy during the incongruent Stroop trials ($r = 0.26$, $p = 0.002$) that agrees with the evidence that increased crosstalk between these two cortical regions is involved in implementing behavioral adjustments during task conflict (e.g., Kerns et al., 2004).

3.4.5 Mediation Effects of dACC and DLPFC Functional Connectivity on Emotion Regulation and the Metabolic Syndrome

In these exploratory mediation analyses, we found that the positive dACC-DLPFC connectivity significantly mediated the relationship between reappraisal use and the MetS (*ab* indirect effect = -0.2163, 95% CI = -0.5368 to -0.0203; see Figure 10) after adjusting for age, gender, and suppression use. Based on the direction of the paths, these mediation effects suggest that individuals who frequently use cognitive reappraisal may be at lesser MetS risk in part via an enhanced capacity to recruit prefrontal brain circuits when negative affective states demand cognitive control.

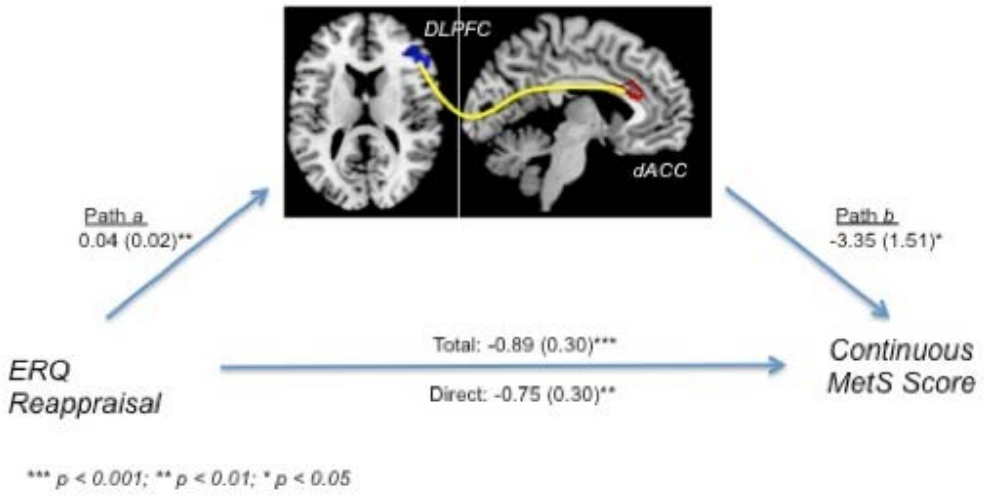

Figure 9. Mediation results with PPI analyses.

Bootstrapped paths show that dACC-DLPFC functional connectivity during incongruent conditions, mediated the inverse relation between reappraisal use and continuous MetS score.

4.0 DISCUSSION

The process model of emotion regulation supports the hypothesis that individual differences in the use of reappraisal and suppression could plausibly relate to negative cardiovascular health outcomes (DeSteno et al., in press; John & Gross, 2004; Mauss & Gross, 2004). However, no studies have yet characterized the potential neural pathways through which different forms of cognitive emotion regulation may relate to measures of cardiovascular health (DeSteno et al., in press). Accordingly, the goal of the present study was to characterize neural activity changes in brain regions that support cognitive control processes and presumably emotion regulation processes and then link these neural changes to individual differences in self-reported reappraisal and suppression, as well as to three measures of the MetS. First, cognitive reappraisal use was inversely associated with the MetS; suppression was not associated with the MetS or associated components. Second, increased cognitive reappraisal use and the reduce likelihood of having the MetS covaried with a more positive functional connectivity between the dACC and DLPFC. Third, and more importantly, this positive dACC-DLPFC connectivity mediated the association between cognitive reappraisal use and the MetS, such that individuals who frequently use cognitive reappraisal may be at lesser MetS risk in part via an enhanced capacity to recruit prefrontal cognitive control systems during negative affective states.

Our first set of findings indicates that individuals who habitually use reappraisal were less likely to have the MetS. There was also evidence that inter-individual variation in

reappraisal use was specific to central adiposity and dyslipidemia. However, it is noteworthy that individuals meeting an increasing number of MetS criteria showed a graded reduction in reappraisal use, which implies that the aggregate clustering of multiple MetS components relates, in a dose-response manner, to less frequent use of presumably adaptive cognitive strategies to regulate negative emotion. Further, there was an inverse relationship between reappraisal use and the continuous MetS score that is thought to reflect one's overall cardiometabolic risk. Together, these results are consistent with a 6-year prospective study showing that trait-like use of cognitive emotion regulation predicts reduced presence of the MetS (Kinnunen et al., 2005).

The affective and cognitive consequences of cognitive reappraisal may represent two possible pathways through which this specific emotion regulation strategy might relate to negative cardiovascular health outcomes (John & Gross, 2004). With respect to affective consequences, appraisals of potentially negative situations could serve to initiate the emotional experience and/or reframe the emotional meaning of these situations (Gross, 1999; Lazarus & Folkman, 1984; Lazarus, 1966). Reappraising negative or otherwise distressing situations with cognitive reappraisal strategies has been shown to diminish negative affect as well as increase positive emotions (Gross & John, 2003; Webb et al., 2012). Hence, individuals tend to consider cognitive reappraisal (as opposed to behavioral suppression) as an adaptive emotion control strategy when regulating negative emotions, as it reduces the subjective experience of negative affect, enhances cognitive resources, and the evokes no pronounced effects on the autonomic components of emotional responding (Gross, 2002; Nezlek & Kuppens, 2008; Webb et al., 2012). Along these lines, given the increased prevalence of negative emotionality among individuals with the MetS (Tamashiro, 2011), there is reason to believe that typical use of adaptive reappraisal strategies might demonstrate an inverse association with the MetS by

resolving the unhealthy subjective, behavioral, and physiological pathways through which negative emotions influence risk for the MetS (Goldbacher & Matthews, 2007). This adaptive role of cognitive emotion regulation strategies, such as reappraisal, within the context of CVD risk may be imparted through a range of cognitive control abilities that help maintain an emotional appraisal of a situation in mind (working memory), inhibit the proponent emotional response regarding the situation (response inhibition), create different interpretations of the situation (working memory), monitor subjective affect to track the efficacy of the regulatory strategy (performance monitoring), and monitor for conflicts between early emotional appraisal and cognitively restructured (conflict monitoring; Ochsner & Gross, 2008). Indeed, reappraisal use to reduce negative affect presents minimal 'cognitive cost' to the individual (Gross, 2002; John & Gross, 2004) and has been shown to actually prime cognitive resources through the enhancement of memory and cognitive control functions (Moser, Most, & Simons, 2010). That being said, the capacity to integrate these cognitive control abilities may facilitate the efficient use of cognitive reappraisal, with recent reports showing that individual differences in working memory capacity, set-shifting, and response inhibition might collectively be involved in reappraisal (Joormann & Gotlib, 2010; McRae et al., 2012; Schmeichel et al., 2008). Interestingly, deficits in these cognitive control abilities are characteristic among individuals with the MetS, with converging neurobiological evidence suggesting that the executive function impairments in the MetS may reflect alterations in cognitive control brain regions (Hoth et al., 2011; Yates et al., 2012) that support a broad range of hierarchical cognitive processes implicated in reappraisal (Niendam et al., 2012). In sum, the cognitive control processes through which affective and cognitive pathways converge to influence the relations between reappraisal

and MetS risk may provide some insight into the possible prefrontal and cingulate brain regions that support emotion regulation (Ochsner et al., 2012).

Consistent with this view of reappraisal engaging various forms of cognitive control that are typically unrelated to emotion, our finding that positive functional connectivity of the dACC and right DLPFC was correlated with increased cognitive reappraisal use suggests that individuals who make repeated use of reappraisal might engage a neural circuitry implicated in processing conflict that is largely cognitive (Mohanty et al., 2007). Based on the functional distinction between ACC subregions, the increased recruitment of this dACC response within this cortico-cortical network by high reappraisers may reflect the initial use of cognitive, rather than emotional, cues from the environment to guide subsequent behavior, which accords with the notion that incongruent color-word stimuli represents two conflicting sources of information contained within the color word and the ink color that are identified by the dACC (Ridderinkhof et al., 2004). Although there is evidence (Kerns et al., 2004; Ridderinkhof et al., 2004) that dACC can take on a dual-role in both monitoring for response conflict and adjusting subsequent behavior, conflict models indicate that the dACC signals DLPFC regions when additional cognitive control abilities are required to adjust behavior through goal-driven attentional process. In the context of emotion regulation, the link between cognitive reappraisal and positive dACC-DLPFC connectivity is consistent with neural models of emotion regulation that highlight cortico-cortical connections between dACC and lateral PFC regions support various cognitive control processes (i.e., selective attention, performance monitoring, and planning) involved in automatic regulation of emotion (Ochsner & Gross, 2005; Phillips et al., 2008). Moreover, since cognitive reappraisal involves integrating various cognitive control processes in order to focus attention on and monitor motivationally relevant stimuli, it is plausible that the neural pattern of

activity among individuals who typically use reappraisal would show functional relationships between brain regions that are implicated in specific cognitive control processes. Interestingly, the functional role of this dACC-DLPFC connectivity was highlighted in another study that found individual differences in the ability to cognitively process one's emotional state was positively associated with increased functional connectivity between dACC and right DLPFC during an emotion decision-making task. Together with our results, this dACC-DLPFC cognitive control network might be broadly involved in implementing executive control processes that guide attention to either salient cognitive or emotional cues that require effortful decision-making. In this regard, it is notable here that we failed to replicate prior studies (Drabant et al., 2009; Vanderhasselt et al., 2013) that found a relationship between cognitive reappraisal and neural activity within individual ROIs across prefrontal and cingulate regions. These initial studies reported that individual differences in reappraisal use correlates with increased activity within similar prefrontal cortical regions that are engaged by the Stroop incongruent condition, including DLPFC, dACC, and lateral OFC (Drabant et al., 2009; Vanderhasselt et al., 2013). Hence, this raises questions as to why we failed to find an association between the tendency to use reappraisal and activation in any isolated PFC region.

There are several reasons to explain the null finding between prefrontal and cingulate ROIs and reappraisal in our sample. First, the two earlier studies utilized fMRI paradigms that involved perceptual processing of emotional material. Drabant et al. (2009) employed a task that had participants process emotionally negative facial expressions. Similarly, Vanderhasselt et al. (2013) used a task that required participants to inhibit a dominant response to negative emotional information in favor of an opposite emotion. The negative emotionally of these two tasks indicates that, to some extent, several cognitive emotion regulatory processes were being taxed,

especially in the Vanderhasselt et al. (2012) study, where individuals had to utilize cognitive control abilities in order to inhibit the prepotent emotional response. Since participants had to focus on emotional cues in order to perform these task, it is likely that prefrontal and cingulate activity within these two studies reflect a greater degree of cognitive control of negative emotion than an effortful cognitive task, such as the Stroop. Additional support for this need to control negative emotions within these studies is reflected in the robust amygdala response that both tasks elicited. The absence of an amygdala response during the incongruent Stroop condition suggests that reappraisers may not have been engaging in any explicit emotion regulation aimed at down-regulating negative affect. In contrast, Drabant et al. (2009) found reappraisal use was inversely related to amygdala activity during threat-related processing while Vanderhasselt et al. (2013) showed that amygdala activity increased while disengaging from negative faces among individuals who use expressive suppression regulatory strategies. Hence, from these two studies, it is possible that observed activation in prefrontal cortical regions is more proximally related to emotion-related reappraisal functions, given the need to process and inhibit negative emotional information in their fMRI paradigms. In contrast, the activity in our prefrontal and cingulate regions most likely reflects "cold" cognitive control activations that may not be as proximal to the explicit function of cognitive reappraisal strategies, which is to reframe an affectively charged situation into unemotional terms (Ochsner & Gross, 2008).

The observation that habitual reappraisal use relates to the MetS may have significance for interventions targeted at resolving adverse health behaviors that contribute to the MetS and possibly CHD risk (Vitaliano et al., 2002). Specifically, studies of health behaviors have begun to highlight how individual differences in the capacity to regulate emotion can alter the psychological distress and negative emotional processes that often relate to poor health

behaviors, such as tobacco use and high carbohydrate intake unmet by commensurate expenditures of energy. Interestingly, our findings agree with the association between emotion regulation and health behaviors given that we found a neural circuitry within dACC and DLPFC brain regions involved in cognitive control of behavior statistically mediated the link between reappraisal and the MetS. This dACC-DLPFC control network is consistently implicated in monitoring and implementing adjustments in behavior in the face of conflict processing. Thus, this dACC-DLPFC circuit may represent a neurobiological pathway through which individuals who typically use reappraisal may engage in adaptive health behaviors that are inversely associated with risk for the MetS. For example, among depressed adult smokers, less frequent use of reappraisal was associated longer smoking duration and more cigarette puffs (Fucito, Juliano, & Toll, 2010). Similarly, a recent study found that relative to cognitive reappraisal, suppression of emotion covaries with poor eating behaviors, namely increased intake of 'comfort' foods (Evers, Marijn Stok, & De Ridder, 2010). Further, adaptive emotion regulation strategies, such as reappraisal, have been shown to decrease the desirability of craved food (Giuliani, Calcott, Berkamn, 2013) as well as the consumption of food following a negative emotional experience (Taut, Renner, & Baban, 2012). Consistent with these behavioral studies, several neuroimaging studies have shown that measures of activity within nodes of this dACC-DLPFC circuit are linked to decreased craving for food and cigarettes as a result of cognitive reappraisal (Kober et al., 2010; Zhao et al., 2012). Taken together, it appears that prefrontal and cingulate activity associated with use of reappraisal strategies covaries with adaptive health behaviors that reduce risk for the MetS. This suggests that a behavioral pathway may underlie the inverse relation between dACC-DLPFC connectivity and the MetS.

At this stage, it is important to highlight several limitations of this study. We tested a putative meditation model that functional variation in cognitive control brain systems would partly account for the association between cognitive reappraisal and the MetS. However, our cross-sectional design does not support causal inferences within this model, nor does it permit the exclusion of other neurobiological explanations of our study outcomes. Experimental and longitudinal designs will help tease apart the directionality of these associations and mediation effects reported here in addition to providing a more comprehensive assessment of potential confounders or effect modifiers. The possibility of various 'third-factor' explanations will also be important to address in the context of multimodal neuroimaging studies that incorporate positron emission tomography (PET) imaging. For instance, future work could explore the variability in central serotonergic and dopaminergic modulatory systems, with existing reviews highlighting within various animal species, including humans, that these monoamine systems are linked to individual differences in regulatory coping styles (Koolhaas, De Boer, Coppens, & Buwalda, 2010). In relation, the MetS has been associated with central alterations in these two monoamine systems (Muldoon et al., 2004, 2006; Rubi & Maechler, 2010; Williams et al., 2010), which furthers the notion that other neural pathways could account for the association between different forms of emotion regulation and the MetS. Another limitation was examining typical reappraisal use in association with just one fMRI task—namely, processing of conflictual color-word information. The use of the Stroop color-word task was based on its ability to robustly activate cognitive control brain circuitry and evoke subjective psychological distress (Sheu et al., 2012). Hence, the Stroop task would appear to be appropriate for probing whether functional variation in cognitive control system activity covaries with indicators of the MetS, and by extension possibly links habitual reappraisal use to such indicators given its increasing use in

cognitive neuroimaging as an assay of cognitive control and interference resolution (Nee et al., 2007). However, despite the subjective frustration and negative affect that the Stroop task elicits, the current fMRI findings that cognitive reappraisal covaries with increased dACC-DLPFC connectivity patterns cannot be interpreted from an emotion regulation standpoint. In light of this, additional work is needed to determine whether individual differences in typical reappraisal use engages neural response during an emotion regulation paradigm wherein reappraisal of negative stimuli is instructed and voluntary. Prior research has shown that reappraisers exhibit increased recruitment of control-related prefrontal regions that appears to down-regulate activity in emotion-generative limbic regions (Drabant et al., 2009). Moving forward, future studies might benefit from examining typical reappraisal use in the context of an explicit emotion regulation task so as to determine whether cortico-cortical connectivity patterns exist during the processing and integration of cognitive and emotional stimuli. Specifically, it is possible that some degree of implicit, automatic emotion regulation may have occurred while individuals performed the Stroop task given that reappraisal was linked to increased valence following the cognitive stressor task. Hence, additional work will help distinguish whether this dACC-DLPFC connectivity pattern reflects reappraisal-related activation or more broad cognitive control processes (Niendam et al., 2012). Lastly, although these findings prove novel, we are left to speculate on how increased dACC-DLPFC connectivity associates with cardiometabolic outcomes. There is considerable evidence from the health behavior literature that individual differences in dACC and DLPFC functioning is linked to smoking and excess eating. However, this study lacks the relevant measures of physiology to able to characterize whether autonomic and neuroendocrine pathways link cortical brain function to MetS.

These limitations notwithstanding, the present set of results support the notion that cognitive reappraisal strategies may relate to MetS risk. Further, individuals who use reappraisal in everyday life appear to strongly engage a cognitive control neural network during a demanding executive function task that is associated with implementing conflict-monitoring functions and behavioral adjustments in action plans (Kerns et al., 2004). Since the Stroop task did not explicitly call for reappraisal, it is also possible that individuals who habitually use cognitive reappraisal may recruit automatic forms of cognitive control represented in prefrontal and cingulate brain regions that exert regulatory self-control processes that are not always targeted towards emotion regulation per se (Ochsner & Gross, 2008). Although the present fMRI results to do not extend to explicit forms of emotion regulation, the findings highlight a distinct non-affective cognitive control pathway that reappraisers may recruit in order to exert control over maladaptive health behaviors and perhaps aspects of peripheral physiology related to the MetS.

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