Intrinsic Spirituality and Acute Stress: Neural Mechanisms Supporting the Relationship Between Spirituality and Reduced Stress Responsivity

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Abstract

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Spirituality is a multidimensional construct that refers to the experience of self-transcendence and connection with a higher sacred reality. Previous research has demonstrated that spirituality represents a consistent resilience factor for stress and a range of stress-related mental disorders, but neural mechanisms by which spirituality confers resilience are unknown. This paper focuses on intrinsic spirituality, or the extent to which spirituality functions as a master motive in one's life regardless of religious affiliation, and reviews the research literature on behaviors and brain structures and functions related to intrinsic spirituality. Additionally, literature is reviewed on adaptive and maladaptive functions of the stress response, its relationship to psychopathology, and its underlying neurobiology. To understand neural responses underlying the link between intrinsic spirituality and stress, the current study utilized a script-guided imagery task to assess brain activity during a stress exposure. Results showed that during a stressful experience higher intrinsic spirituality is associated with greater deactivation in the hippocampus, brain stem, ventral striatum, thalamus, extending to the orbitofrontal cortex (OFC) and ventromedial prefrontal cortex (vmPFC), as well as in another cluster comprising of the posterior cingulate cortex (PCC) and right inferior parietal lobule. These regions are implicated in stress responsiveness, emotional and cognitive

processing, and self-referential processing. While preliminary, results provide a potential neural substrate for how spirituality may influence stress processing. Moreover, they suggest a role for spirituality in attenuating neural responses to stress responsivity, regulating emotion during exposure to stress, and preventing and treating stress-related psychopathology.

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Introduction

Spirituality cannot be defined by scientists in an ultimate sense, but its constituent dimensions can be examined by science as having biological correlates and an impact on behavior and health. In this inquiry, the human experience of spirituality refers to a capacity through which one experiences self-transcendence and connection with a sacred reality, typically regarded with ultimate concern (Eliade, 1959; Emmons, 1999; Otto, 1958; Tillich, 1957). Stress represents any disruption to an individual's psychological homeostatic processes and can take a range of forms from major traumatic events to daily hassles (Burchfield, 1979; McEwen, 2016). While the stress response is often an adaptive feature that promotes protection against outside threats (Bonanno, 2004; De Kloet et al., 2005; Luthar et al., 2000), research shows that maladaptive responses to stress over time also represent a significant etiological factor for a range of mental disorders (Cohen et al., 2007; De Kloet et al., 2005; Faravelli et al., 2012; Kwako & Koob, 2017). In addition, researchers have found that spirituality has an inverse relationship with perceived stress (Southwick & Charney, 2012; Strawbridge et al., 1998). However, the neural mechanisms by which spirituality may confer resilience to stress are unknown. This paper focuses on intrinsic spirituality, a trait characterized by personal importance and overarching motivation of spirituality in one's life, and reviews the research literature on how it relates to other spirituality variables, behavioral outcomes, and brain structure and function. Furthermore, literature is reviewed on adaptive and maladaptive functions of the stress response, its relationship to psychopathology, and its underlying neurobiology. Preliminary functional magnetic resonance imaging (fMRI) data are presented that show a potential neural substrate for how spirituality may influence stress processing. While preliminary, these findings suggest a role for spirituality in attenuating stress responsivity and regulating emotion during exposures to acute stress.

Spirituality and Religion

For the vast majority of the world's population, spiritual and religious concerns play a prominent role in people's lives (Gallup, 1999; Walsh, 2011). While both spirituality and religion are highly overlapping constructs that refer to self-transcendence and connection with a higher power and sacred dimension of existence (Eliade, 1959; Emmons, 1999; Hodge et al., 2015; Otto, 1958), scholars generally agree that religion refers more to institutionally held sets of beliefs, sacred texts, traditions, and practices contextualized by culture, which can support and cultivate the human capacity for spirituality (Carroll, 1997; Koenig, 2012; Zinnbauer et al., 1997). While individuals typically describe religiosity in terms of personal beliefs about God or a higher power, organizational practices like church attendance, and an adherence to a collective belief system, spirituality is typically associated with more personal, experiential, and relational descriptions of one's connection to God or a higher power (Pargament et al., 1995). Research has found that religiosity is correlated with higher levels of adherence to religious orthodoxy, deference to authority, religious attendance, and parental religious attendance, while spirituality is correlated with higher levels of mystical experiences and non-orthodox belief, as well as hurtful experiences with religious leaders (Hood et al., 1996; Roof, 1993; Zinnbauer et al., 1997). Generally speaking, a more spiritual orientation can co-exist with a wider range of cultural and religious worldviews. For example, there is a significant number who understand their spirituality in non-theistic terms, including but not limited to adherents of Buddhism (Richards & Bergin, 1997). A growing number of individuals also consider themselves spiritual but not religious. This group is more individualistic than their spiritual and religious counterparts and tends to conceptualize religiosity and spirituality as distinct and non-overlapping (Zinnbauer et al., 1997).

Despite real distinctions, most people who consider themselves religious view themselves as spiritual and vice-versa (Zinnbauer et al., 1997), and research has found a moderate to high degree of correlation between religiosity and spirituality (r = 0.4 to 0.9), depending on the measures used (Hodge, 2003; Kass et al., 1991; Saucier & Skrzypińska, 2006). Furthermore, both spirituality and religion share a number of essential features in common that include personal salience of spirituality/religiosity, private contemplative and prayer practices and related altered states of consciousness, compassionate and altruistic engagement, and virtues and character traits (Benson et al., 2012; Emmons, 2000; McClintock et al., 2016; Wilber, 2006).

Intrinsic Spirituality

In the 1960's, Gordon Allport developed the notion of intrinsic religiosity, which became a classic and well-researched construct in the social scientific field of religion (Allport, 1950). In contrast to extrinsically religious individuals who approach religion instrumentally for other reasons like social acceptance or self-justification, those who are intrinsically religious posit their connection to God or a higher power as an organizing theme and motivational force in their lives (Allport & Ross, 1967; Pargament, 1999). As such, the construct of intrinsic religiosity can be understood as capturing one's internalized spiritual commitment within an explicitly religious framework (Burris, 1999).

David Hodge some decades later revised this classic construct to become more inclusive of those who are not necessarily religiously affiliated or do not necessarily subscribe to doctrinal beliefs yet, nevertheless, prioritize spirituality in their life (Hodge, 2003). Thus, Hodge's construct of intrinsic spirituality modifies Allport's intrinsic religiosity to capture the degree to which spirituality is personally important and serves as a motivating influence in one's life both within and outside of a religious context or framework (Kass et al., 1991; Spalding & Metz, 1997). In Hodge's instrument, the Intrinsic Spirituality Scale (ISS), items from Allport and Ross' (1967) original Religious Orientation Scale (ROS) were revised to specifically assess a broader notion of spirituality while staying consistent with their original underlying notion of an intrinsic motivation (Hodge, 2003; see also Appendix). Thus, the ISS measures a very similar yet broader and more inclusive construct that counts the growing numbers of people who do not identify as religiously affiliated yet consider themselves spiritually oriented, as well as those who may be religiously but non-theistically oriented (Dilmaghani, 2018; Hay, 2013; Putnam & Campbell, 2012). The ISS has demonstrated validity across multiple religious groups as well as in other sub-populations like health providers (Gough et al., 2010; Hodge, 2003; Hodge et al., 2015). For intrinsically spiritual people, their connection with a transcendent and sacred dimension of existence, by whatever name, informs all other dimensions of life. They locate their ultimate life purpose within the context of their spirituality. Spirituality for these individuals is the highest priority, functioning as a master motive that guides values, decisions, growth, and all other aspects of their lives (Hodge, 2003).

Though the number of studies that utilize the ISS is limited, research has linked intrinsic spirituality to a variety of salutary outcomes. Among at-risk youth, intrinsic spirituality was associated with a lower frequency of delinquency behaviors such as carrying a weapon, destroying property, and creating a public disturbance, as well as less public drunkenness and binge alcohol (Salas-Wright et al., 2013a; Salas-Wright et al., 2013b). Intrinsic spirituality of spinal cord injured patients predicted greater resilience over the course of inpatient rehabilitation (White et al., 2010). Among low-income job seekers, intrinsic spirituality predicted greater hope and, mediated by hope, indirectly affected employment self-sufficiency (Hong et al., 2015). Intrinsic spirituality has been linked with higher ethical idealism and lower ethical relativism in business people (Kolodinsky et al., 2010). Among older adults, intrinsic spirituality has also predicted overall well-being (Hilton & Child, 2014).

Measures Similar to the Intrinsic Spirituality Scale (ISS)

Two other psychometric instruments that measure the degree to which people prioritize their spirituality and/or religiosity feature prominently in the literature: the aforementioned ROS, which captures the significance of religion as a master motive in one's life, and a single-item measure of personal importance of religion or spirituality (Allport & Ross, 1967; Koenig et al., 2012). After more than 50 years, the ROS is still in widespread use and has spawned a number of modified versions (Hill & Hood, 1999; Williams, 1994). Research has found that scores on the ROS predict a number of positive qualities like empathy, altruistic behavior, self-efficacy, and subjective happiness (Beit-

Hallahmi & Argyle, 1997; Ventis, 1995; Watson et al., 1984). Intrinsic religiosity has also been shown to correlate with a greater number of character strengths including kindness, leadership, and forgiveness, as well as a higher frequency of volunteer service (Ahmed, 2009; Johnson et al., 2013). Intrinsic religiosity is also related to greater self-control (Mccullough & Willoughby, 2009; Richards, 1994; Watterson & Giesler, 2012). One investigation found that study participants high in intrinsic religiosity persisted with highly challenging anagram tasks longer than those low in intrinsic religiosity, but only after first completing a resource depletion task (Watterson & Giesler, 2012). The greater levels of self-control may be explained by psychological and behavioral demands placed upon religious practitioners—such as regularly attending religious services, practicing meditation and prayer, and monitoring and adjusting behavior according to religious mores and guidelines—that could contribute to strengthening the capacity for self-regulation (Mccullough & Willoughby, 2009; Watterson & Giesler, 2012). Intrinsic religiosity is also associated with better mental health outcomes including lower rates of worry, guilt, depression, and suicide (Cotton et al., 2006; Koenig et al., 2004; Mccullough et al., 2000; Ventis, 1995). One study found that intrinsic religiosity, but not religious attendance or private religious activities, predicted shorter time to remission among patients with major depressive disorder (Koenig et al., 1998). A meta-analytic study examined 42 previous studies and found that intrinsic religiosity was associated with lower all-cause mortality (Mccullough et al., 2000).

Another highly similar and oft-used measure is a single item in which participants are asked to rate on a four-point scale (1=not important at all; 4=highly important) the following: “How important to you is religion or spirituality?” (Koenig et al., 2012). In a large nationally representative sample in Canada, those who stated that religion or spirituality was highly important to them were more likely to feel they belonged to a larger community, to feel they contributed to society, and to believe society improves for people like them. This group also agreed more than all others that life has meaning and that life challenges make them better people (Dilmaghani, 2018).

In a series of studies of individuals at high and low familial risk for major depression, those who reported that religion or spirituality was highly important to them had approximately one-quarter the risk of experiencing major depression in the ensuing ten years compared with other participants. Furthermore, among those in the high risk group, participants who reported a high importance of religion or spirituality had about one-tenth the risk of having major depression (Miller et al., 2012). Additionally, for those with a high number of previous negative life events compared to others, high importance of religion or spirituality was associated with one-quarter the risk of having any mood disorder ten years later (Kasen et al., 2012). Overall psychosocial functioning was associated with higher levels of importance of religion or spirituality (Kasen et al., 2014). A previous diagnosis of major depression also predicted lower importance of religion or spirituality five years later (McClintock et al., 2018). In a large multinational study, the more important one considered religion or spirituality in one's life, the higher the level of quality of life, satisfaction with life, and health behaviors (Moons et al., 2019).

While the importance of religion or spirituality item, the ROS, and the ISS differ slightly in their particular focus and language, they capture highly similar constructs that assess the degree to which people’s connection to transcendence and the sacred is salient in their life. A significant body of research supports the notion that personal importance of a transcendent, sacred reality is associated with positive states of mental health and behaviors.

Brain Function and Structure Related Intrinsic Spirituality

Despite the evidence that intrinsic spirituality and highly similar traits are related to a wide range of salutary behavioral and mental health outcomes, to date only limited data exist for brain mechanisms that underlie these processes (Puchalski, 2010). In one structural MRI study in a sample of individuals at high and low familial risk for depression, importance of religion or spirituality was shown to correlate with cortical thickness in parietal and occipital regions bilaterally, as well as the right mesial frontal lobe and the left cuneus and precuneus (Miller et al., 2014). Because these regions also showed cortical thinning among those with high familial risk of developing depression (Peterson et al., 2009), this finding revealed brain structures and neural pathways that might link religion or spirituality with a reduced risk for depression. Liu and colleagues (Liu et al., 2017) subsequently showed in the same sample that importance of religion or spirituality was associated with a thicker cortex in the left superior frontal gyrus among individuals at high risk. Additionally, larger pial surface areas were associated with regions that include the left isthmus cingulate, middle temporal gyrus, precentral gyrus, lateral occipital complex, rostral middle frontal gyrus, superior frontal cortex, right inferior parietal lobule, inferior temporal cortex, superior frontal gyrus, and superior temporal cortex. Greater important of religion or spirituality among people at high risk for depression also correlated with decreased DMN connectivity (Svob et al., 2016). These studies were among the first to demonstrate a plausible neurobiological link between self-rated importance of religion or spirituality and psychopathology.

In a virtual lesion study, inhibiting the inferior parietal lobule using transcranial magnetic stimulation was followed by an increase in implicit importance of religion or spirituality as measured by the Implicit Association Test, demonstrating a causal role for the inferior parietal lobule in alterations of religious or spiritual self-representation (Crescentini et al., 2014). In response to making mistakes, a group of religiously oriented individuals compared to those not religiously oriented demonstrated less distress and reduced reactivity in the anterior cingulate cortex (ACC), suggesting a role for religiosity in buffering emotional reactivity (Inzlicht et al., 2009). In a separate investigation, researchers found that among religiously oriented individuals self-evaluations involved less activation in the inferior parietal cortex and precuneus, suggesting that the perceived self-other distinction may be more diffuse among those religiously oriented (Han et al., 2008). In an EEG study, participants who rated religion or spirituality as highly important at initial assessment showed greater posterior alpha ten years later compared to those who did not, suggesting a neural marker for ontogenesis of religion or spirituality (Tenke et al., 2013). In a follow-up study, these results were maintained 20 years after the initial assessment (Tenke et al., 2017).

Stress and the Stress Response

While the concept of stress may seem intuitive, stressors come in a variety of different forms ranging from loss of loved ones to interpersonal abuse, from physical dangers to social isolation, from major traumatic events to daily hassles (Hammen, 2005). Stressors can be mild or severe, predictable or unpredictable, and can occur in a wide variety of contexts (Kretz et al., 1999). While it can take a multiplicity of forms, stress fundamentally represents any disruption to an organism’s necessary psychological homeostatic processes (Burchfield, 1979; McEwen, 1998).

The stress response represents the ways in which an organism mobilizes to respond to a stimulus perceived as harmful and threatening. Typically, the stress response is an adaptive feature that has evolved to protect an organism from outside threats and involves resources from metabolic, cardiovascular, immune, autonomic, and central nervous systems (Franklin et al., 2012). During the response to re-establish homeostasis, rapid activation by stress is quickly followed by recovery (Franklin et al., 2012). In order to return to homeostasis following a stressful event, therefore, the adaptive stress response is limited in duration and amplitude (De Kloet et al., 2005; McEwen & Gianaros, 2011). When an organism responds in a manner that efficiently recruits and terminates allostatic processes, stress can promote adaptive coping and resilience, even potentially leading to positive growth experiences (Karatsoreos & McEwen, 2011). This appropriate and adaptive response to stress is required for sustained mental health in the face of adversities and for reducing psychopathology after exposure to severe or chronic stressors (Rutten et al., 2013). Over time, resilient individuals typically develop and strengthen adaptive psychological responses and learn to perceive adversities as minimally threatening (Del Giudice et al., 2011).

However, stress can also trigger an insufficient or poorly organized response, which can lead to allostatic load and deleterious consequences on mind and body. Allostasis is an active process that supports physiological, phenomenological, and behavioral stability during change (Franklin et al., 2012). When perceived environmental demands overwhelm the adaptive capacities of an organism through acute trauma or repeated stressors, it can result in a delayed response to stress and, eventually, allostatic load (Cohen et al., 2007; McEwen et al., 2015). Allostatic load, in turn, can cause wear and tear on the body and brain, as well as contribute to mental and physical disease (McEwen, 1998; McEwen & Wingfield, 2003). Individuals have starkly differing levels of susceptibility to the deleterious consequences of stress, factors of which include personality traits, previous traumatic life events, epigenetic mechanisms, and the microbiome (Magalhaes et al., 2018). Within more vulnerable individuals, insufficient and inappropriate stress responses can over time morph into a chronic state of stress. While the underlying mechanisms of stress, vulnerability, and resilience are thought to depend on a complex combination of genetic and nongenetic factors, such mechanisms are not well understood (Franklin et al., 2012).

Neurobiology of Stress

Nevertheless, it is well known that the nervous system plays a crucial role in coping with the demands of stress (McEwen, 2016). The dynamic and widely distributed neural circuitry of the nervous system coordinates and regulates behavioral and allodynamic response systems. Biological pathways of the stress response particularly within the sympathetic adreno-medullary system (SAM) and hypothalamic-pituitary-adrenal axis (HPA) have been well-documented (Sinha, 2008). Immediately following a stress induction, dynamic interactions between the SAM and HPA systems induce a hypervigilant state which can optimize detection of outside threats (Dolcos, 2014; Henckens et al., 2009; Hermans et al., 2014). The SAM system is involved in the initial and rapid phase of the stress response, often considered the “alarm reaction” or the “fight-or-flight” response. When the autonomic nervous system first becomes activated, the adrenal medulla releases epinephrine and norepinephrine. These hormones rapidly decrease heart rate variability and increase basal metabolic rate, blood pressure, and respiration, skin conductance, pupil diameter, and blood flow to organs essential to the "fight-or-flight" response, such as skeletal muscles and the heart (Lucassen et al., 2014; Van Oort et al., 2017).

After this quick initial stage, the HPA axis also becomes active but in a more gradual fashion. Activation of the HPA axis is initiated by stimulation of neurons in the paraventricular nucleus of the hypothalamus. Corticotropin-releasing hormone and arginine vasopressin are then secreted from the portal vein of the hypothalamus. The pituitary gland releases adrenocorticotropic hormone, after which the adrenal cortex secretes glucocorticoids and the adrenal medulla secretes adrenaline and noradrenaline into the bloodstream (Franklin et al., 2012). As a consequence of this elaborate neuroendocrine circuit, cortisol levels in the bloodstream rise, adaptive physiological responses are modulated, emotional and cognitive responses are coordinated, and psychological homeostasis is re-established (Lucassen et al., 2014; Smith & Vale, 2006; Van Oort et al., 2017).

As previously indicated, apart from its adaptive features, the stress response may also be insufficient, excessive, or prolonged (De Kloet et al., 2005; McEwen & Gianaros, 2011). While short-term cortisol elevations are adaptive, sustained increases in cortisol can result in allostatic load, which can have deleterious effects on HPA axis function. Specifically, allostatic load can lead to long-term hypercortisolemia, which has harmful consequences that include impairment of neurogenesis (Rutten et al., 2013). Additionally, biochemical changes over time can result in reduced basal cortisol response (Clow et al., 2010), the long-term consequence of which includes increased risk for mental disorders (Cohen et al., 2007; McEwen, 1998).

In addition to the SAM and HPA systems, certain regions and circuits in the central nervous system play a vital role in the response to environmental stressors and subsequent experience of distress. Specifically, the amygdala, hippocampus, insula, and cingulate, orbitofrontal, and medial prefrontal cortices are involved with perceiving and appraising stressful stimuli, while the brain stem, hypothalamus, striatum, thalamus, and other limbic regions are implicated in physiological and emotional responses (López et al., 1999; Sinha, 2008; Sinha et al., 2004; Zhou et al., 2008). Additionally, during anticipation of stressors, the amygdala and striatum, in particular, have been found to have a large role (Koob & Le Moal, 2008; Ledoux, 2000; Seo et al., 2011). Thus, a large-scale corticostriatal-limbic circuitry is involved in processing threats, anxiety, and fear and in preparing individuals for the fight, flight, or freeze response.

Continuous stimulation of this corticostriatal-limbic circuit by chronic or overwhelming stress, however, could lead to maladaptive patterns in the brain and dysregulation of neural circuitry (Carrion & Wong, 2012). In such conditions, maladaptive and habitual neural patterns by the amygdala, brain stem, and striatum could become dominant while simultaneously weakening prefrontal regulatory function (Arnsten, 1998; Arnsten et al., 2015; Sinha, 2001). Continual prefrontal regulatory impairment, in a cyclical manner, could further disinhibit amygdala and striatal activity and further increase emotional distress and dysregulation (Seo & Sinha, 2011). Stress also impairs the modulation of catecholamine in prefrontal circuits, which in turn adversely influences executive functions like self-control and working memory (Arnsten

& Goldman-Rakic, 1998; Arnsten & Li, 2005). Such dysfunctional interactions between striatal-limbic regions and prefrontal cortical areas could eventually underlie the pathophysiology of stress-related mental disorders (Seo & Sinha, 2011).

A number of functional and structural MRI studies demonstrate associations between corticostriatal-limbic circuitry and stress, suggestive of its deleterious effects in the brain. Individuals with long-term occupational stress were found to have reductions in gray matter volume in the dorsolateral prefrontal cortex (dlPFC) and ACC (Blix et al., 2013). In another study, those who reported overwhelming and uncontrollable stressors in their lives showed reduced neural responses in the medial prefrontal cortex (mPFC) (Lucassen et al., 2014). Major depressive disordered patients with a history of childhood trauma, compared to those without this history, showed reduced functional connectivity within a prefrontal-limbic-thalamic-cerebellar circuit (Wang et al., 2014). A separate study showed that children with a history of abuse had reduced volume in the medial orbitofrontal cortex and middle temporal gyrus (De Brito et al., 2013). An animal study found that chronic, unpredictable stress was associated with structural atrophy in a large swath of key regions that include prelimbic, cingulate, insular and retrosplenial, motor, somatosensory, auditory and perirhinal/entorhinal cortices, hippocampus, thalamus, dorsomedial striatum, nucleus accumbens, septum, the bed nucleus of the stria terminalis, and several brain stem nuclei (Magalhaes et al., 2018). Among depressed patients, early life stress was associated with reduced local connectivity in the ventrolateral prefrontal cortex (vlPFC) and associated with reduced global connectivity in the dlPFC (Cisler et al., 2013).

During script-driven imagery experiments on stress, activity in regions that include the mPFC, ACC, superior/middle temporal gyrus, posterior cingulate cortex (PCC), precuneus, thalamus, striatum, midbrain, and cerebellum significantly increased during stress, in comparison to a neutral-relaxing condition (Seo et al., 2017; Seo et al., 2011; Seo et al., 2019; Sinha et al., 2004). Overall, evidence indicates that corticostriatal-limbic activation increases in response to stress, which consequently can lead to structural atrophy and reduced functional connectivity within this neural circuit as well as impaired behavioral functioning (Arnsten & Goldman-Rakic, 1998; Li & Sinha, 2008; Mischel et al., 1989; Tice et al., 2001).

A key part of the affected brain circuitry is the motivational pathways of the striatal reward system (Krishnan et al., 2007; Sinha, 2008). Greater activity in the striatum has been shown to correlate with greater levels of stress (Oswald et al., 2007; Pruessner et al., 2004; Sinha et al., 2005), and differing transcriptional programs in nucleus accumbens and the ventral tegmental area of the midbrain have been shown to accompany varying levels of resilience and susceptibility to stress (Krishnan et al., 2007). Striatal activity is also related to habitual responses to emotional stimuli (Schultz, 2006; Vink et al., 2005). In rats, for example, chronic stress exposure increases and eventually compromises striatal functioning (Rossi et al., 2008), thereby altering striatal projections to the frontal cortex and disrupting prefrontal executive functioning (Dias-Ferreira et al., 2009). Consistent with these findings, a positron emission tomography study of adults found that dopamine release in the ventral striatum during exposure to stress was related to early life parental care. Specifically, among participants who received low levels of parental care, an acute stressor caused a significantly greater release of dopamine in the ventral striatum, suggesting that resilience to stress is related to decreased firing of dopaminergic projections from the midbrain to the nucleus accumbens (Pruessner et al., 2004). Overall, these brain pathways related to motivation and control are key neuroendocrine targets during stress exposure and reveal potential mechanisms by which stress affects vulnerability to mental disorders (Sinha, 2008).

Hippocampal circuitry, which exerts strong regulatory control over the HPA axis, is also involved with the stress response and has been shown to be damaged by chronic stress (Franklin et al., 2012; Sapolsky et al., 1990). One study found that cortisol levels longitudinally predicted less hippocampal volume in youth (Carrion & Wong, 2012). Chronic stress was also associated with reduced activation in the hippocampus and PFC during memory and executive function tasks (Carrion & Wong, 2012). Furthermore, decreased hippocampal volume and maladaptive functional changes in hippocampal circuitry, as well as associated dysfunctions in glutamatergic neurotransmission, have been shown to correlate with a range of stress-related psychological disorders (Sanacora et al., 2012).

Large-Scale Brain Networks Involved with the Stress Response

During the stress response, regions of the brain do not function in isolation but, rather, are organized into dynamically interacting functional networks, underscoring the need to adopt a systems-level view of brain functioning during stress (Van Oort et al., 2017). Two such large-scale networks, in particular, are significantly involved with the stress response: the salience network (SN) and the default mode network (DMN). The SN—composed of the anterior insula, dorsal ACC, and amygdala and temporal poles primarily, but also inclusive of the ventral striatum, hypothalamus, thalamus, substantia nigra, midbrain, precentral gyrus, and temporoparietal junction (Goulden et al., 2014; Hermans et al., 2011; Seeley et al., 2007)—is involved with the response to salient environmental stimuli as well as emotional processing (Hermans et al., 2014; Hermans et al., 2011; Seeley et al., 2007). Increased activity in this network as well as relevant sensory areas of the nervous system (Van Marle et al., 2009), and increased connectivity between these systems (Li et al., 2014), promote the orienting of attention towards relevant internal or external information (Buckner et al., 2008; Menon, 2011). During acute stress, the SN may also underpin a hypervigilant state (Van Marle et al., 2009), which is adaptive by promoting threat detection to immediate dangers and by decreasing sensitivity to other factors like pain, rewards, and non-relevant stimuli (Hermans et al., 2014; Oei et al., 2014; Yilmaz et al., 2010). Cortisol levels and negative affect are both correlated to within-SN connectivity during and in the aftermath of exposure to stress (Hermans et al., 2011; Van Marle et al., 2010). The other primary large-scale network consistently implicated in the stress response is the default mode network (DMN), whose core regions include the mPFC, PCC, precuneus and inferior parietal lobule (Andrews-Hanna et al., 2014; Buckner et al., 2008; Cavanna & Trimble, 2006; Leech & Sharp, 2013). Although the DMN is much more commonly associated with self-generated thought and self-referential processing, studies show that activity within the DMN increases during stress exposures (Boehringer et al., 2015; Dedovic et al., 2014; Seo et al., 2011; Sinha et al., 2004). Parallel to increased activation in this network, within-DMN functional connectivity also increases in the aftermath of a stress induction (Vaisvaser et al., 2013). Although the precise role of the DMN during acute stress is less apparent than that of the SN, the DMN may become activated when self-referential processing is relevant to the acute stressor (Seo et al., 2011). This notion is supported by a study that demonstrated that social rejection is related to increased DMN activity (Muscatell et al., 2015). Relatedly, DMN disruptions occur in psychopathology. For example, DMN hyperactivity and hyperconnectivity is related to maladaptive rumination in depression (Hamilton et al., 2011).

Inter-network connectivity patterns between the SN and DMN also exist. Increased connectivity between these networks in the resting state after a stress induction is typical in healthy individuals and may reflect adaptive mechanisms in the aftermath of stress (Veer et al., 2011). However, a delay in normalization to a pre-stress exposure baseline may have implications for psychopathology. For example, research has found increased connectivity between the SN and DMN among patients with depression, which may be related specifically to excessive and negative internal processing (Andrews-Hanna et al., 2014).

Implications of the Stress Response for Psychopathology

While a majority of people who are exposed to acute or chronic life stressors do not go on to develop mental disorders (Bonanno, 2004; Luthar et al., 2000; Vinkers et al., 2014), a substantial literature has established a strong link between stressors and psychopathology (Cohen et al., 2007; De Kloet et al., 2005; Faravelli et al., 2012; Kwako & Koob, 2017). Specifically, mental disorders may develop when an individual is unable to adapt to stress exposure (McEwen & Stellar, 1993). Acute and chronic stress, therefore, represents a major etiological factor in the development of a variety of disorders including post-traumatic stress disorder, depression, and substance use disorders.

Researchers have shown that increasing levels of stress are associated with a decrease in behavioral control and an increase in impulsivity and other maladaptive behaviors (Hatzinger et al., 2007; Mischel et al., 1989; Muraven & Baumeister, 2000). Research furthermore suggests that the experience and regulation of both stress and addiction involve highly overlapping brain circuitry (Seo et al., 2011). Indeed, there may be similarities between brain mechanisms of acute stress in healthy states and mechanisms of psychopathology. For example, exposure to acute stress is associated with dissociation within the DMN (Vaisvaser et al., 2016), disruptions in reward processing (Oei et al., 2014), and amygdala hyperactivity in response to emotional stimuli (Van Marle et al., 2009), and very similar brain mechanisms have been found in depression (Mulders et al., 2015), addiction disorders (Balodis & Potenza, 2015), and post-traumatic stress disorder (Fonzo et al., 2010), respectively.

These disorders exert a great toll on the individuals who suffer from them, and their widespread prevalence worldwide represents a significant threat to public health (McEwen & Gianaros, 2011). Thus, the development of improved clinical treatments and preventive interventions that can mitigate the sequelae of psychological stress, as well as a demonstrated efficacy of such interventions within randomized clinical trials would provide data of critical significance and could affect wide reaches of the population (Cohen et al., 2007). Concomitantly, revealing neural mechanisms that underlie the development of vulnerability and resilience to stress and are critical components for developing earlier and more effective interventions for stress-related disorders (Savitz et al., 2013; Southwick & Charney, 2012).

Relationship Between Spirituality and Stress

Within the relatively new but growing scientific field of resilience (Southwick & Charney, 2012), spirituality has been shown to be a consistent resilience factor (Southwick et al., 2005). In a community sample, researchers found that both greater levels of religious commitment and daily spiritual experiences predicted lower levels perceived stress (Reutter & Bigatti, 2014). In a study of pulmonary disease patients, greater levels of spirituality correlated with lower levels of perceived stress (Delgado, 2007). Spirituality also predicted lower perceived stress among engineering students (Yadav et al., 2017). In a study of religious ritual, individuals reciting the rosary compared to those watching a religiously-oriented video experienced lower levels of anxiety (Anastasi & Newberg, 2008).

Researchers have also begun to link spirituality with biological markers of stress. In one study, adults with a higher religious and spiritual commitment had a longer leukocyte telomere length, which has been identified as a biomarker for chronic stress (Hill et al., 2016). Koenig and colleagues (2016) also found that, among caregivers who were at least somewhat religious, telomere length correlated with level of religiosity. Among family dementia caregivers who were randomly assigned to an eight-week meditation group or relaxing music group, those in the meditation group showed 43% improvement telomerase activity compared to 4% improvement in the relaxing music group (Lavretsky et al., 2013). Furthermore, researchers found that telomerase activity was greater in meditation retreat participants than in wait list controls (Jacobs et al., 2011). Spirituality also appears to moderate the relationship between stress and both waist circumference and insulin resistance, as a study found that psychosocial stress predicted waist and insulin resistance only among individuals with a low level of spirituality (Tull et al., 2015).

Intervention studies have also found that spirituality was a key factor in reduced clinical symptoms. For example, one study found that daily spiritual experiences were a key mechanism by which a mindfulness-based stress deduction (MBSR) intervention reduced levels of chronic stress among healthy adults (Greeson et al., 2011). In another MBSR study, daily spiritual experience and mindfulness uniquely explained improvements in depressive symptoms (Greeson et al., 2015). One meta-analysis of mindfulness-based clinical interventions found little evidence of reduced stress (Goyal et al., 2014). However, a separate meta-analysis of MBSR among healthy individuals revealed a nonspecific effect of the intervention on stress reduction compared to an inactive control, both in mitigating stress as well as in enhancing spirituality (Chiesa & Serretti, 2009). In another meta-analysis comparing effects of meditation-based interventions to active controls on various physiological markers of stress, meditation demonstrated reductions in cortisol, blood pressure, heart rate, C-reactive protein, triglycerides and tumor necrosis factor-alpha, providing evidence that the practice of meditation leads to a mitigation of physiological markers of stress across a range of populations (Pascoe et al., 2017). In a study that compared a group who meditated with a group who did not, the meditation group reported less perceived stress and higher plasma dopamine levels, demonstrating that meditation can influence the sympathetic nervous system through dopamine activity (Jung et al., 2010). In another mindfulness-based intervention study, researchers found reduced stress and improved emotion regulation and self-control after the intervention, changes which correlated with increased activity in the ACC and mPFC (Tang et al., 2016).

While some evidence including some preliminary neurobiological data does support a link between higher levels of spirituality and reduced stress, no studies have directly examined the relationship of intrinsic spirituality to stress. Moreover, no research exists on the influence of a person's spirituality during a stress exposure, nor how spirituality may be associated with underlying neural mechanisms during a stress response. Further understanding neurobiological underpinnings of intrinsic spirituality during stress could play an important role in the intervention of a variety of mental disorders including but not limited to post-traumatic stress disorder, depression, and substance use disorders (Grote et al., 2007; Karatsoreos & McEwen, 2011).

Current Study Objectives

Stress is among the most significant risk factors for a range of mental disorders (Dunlop & Liston, 2018), and research strongly supports an inverse relationship between levels of stress and spirituality (De Kloet et al., 2005; Faravelli et al., 2012; Kwako & Koob, 2017). Previously, we reported on the neural correlates of personalized spiritual and stressful experiences using a script-guided imagery fMRI task (Miller et al., 2018). We observed in the spiritual condition relative to a neutral condition reduced activity in the inferior parietal lobule, suggesting that this region may contribute importantly to perceptual processing of spatial and self-other representations during self-transcendent states. Compared with stress cues, responses to spiritual cues also showed reduced activity in the thalamus and striatum, regions that have been implicated in sensory and emotional processing and which were activated during the stressful condition, relative to the neutral condition.

While this investigation yielded data about neural responses to spiritual states in comparison to stressful states, the neural mechanisms by which intrinsic spirituality, a trait characterized by the personal importance and motivation spirituality provides in one's life, may confer resilience to stress have not been investigated. The current study examines how intrinsic spirituality is related to neural underpinnings of the response to acute stress. On the basis of previous research, we expected that intrinsic spirituality would be associated with reduced brain response in corticostriatal-limbic circuitry during acute stress.

Method

Participants

Study participants were recruited via advertisement from New Haven and the surrounding community. Of the 27 adults who performed the fMRI protocol, 24 also completed demographic, cognitive, and psychiatric assessments, including the Structured Clinical Interview for Axis-I Psychiatric Disorders (First et al., 1995) and the Intrinsic Spirituality Scale (ISS) (Hodge , 2003; see Appendix). Two participants met criteria for past major depressive disorder, three participants for past alcohol abuse, two participants for past cannabis abuse, one for past cannabis dependence, and one for past social phobia. All participants had negative urine screens for illicit substances.

Eligibility criteria included that participants had no medical condition or head injury. Participants were excluded if they met any of the following criteria: pregnant, breast-feeding, color-blind, uncontrolled diabetes, history of seizure or neurologic disease, history of cardiovascular disease, BP > 145/90, currently taking antidepressant medication or migraine medication, current substance-use disorder, bipolar disorder, or psychosis. This protocol was approved by the Yale University School of Medicine Human Investigations Committee. All study participants provided written informed consent.

Intrinsic Spirituality Scale (ISS)

The ISS is a six-item scale that measures the degree to which one’s relationship with a transcendent higher power functions as one’s master motive regardless of one’s religious affiliation. Each item is rated on an 11-point scale and uses a sentence completion format to measure attributes related to intrinsic spirituality. A sentence fragment is presented, and two phrases are linked to each end of the 11-point scale, e.g. “When I am faced with an important decision, my spirituality… ‘0=plays absolutely no role’ and ‘10=is always the overriding decision.’” Participants are instructed to select the number that corresponds to their initial feeling along the continuum.

Imagery Script Development Procedures

Approximately one week prior to scanning, personalized guided imagery scripts for spiritual, stress and neutral-relaxing conditions were developed with each participant. The personalized guided-imagery fMRI protocol has previously been described and extensively applied to elicit anxiety and drug and food cravings in a variety of populations (Elsey et al., 2015; Hommer et al., 2013; Jastreboff et al., 2013; Potenza et al., 2012). As previously described in detail (Sinha, 2013), the Scene Development Questionnaire was used to develop the scripts. The specific details that were collected were used to construct a guided imagery script for each condition and then recorded for presentation during the fMRI scan.

Relevant to the current study are the stress and neutral-relaxing scripts, the generation of which were described previously in detail (Elsey et al., 2015; Hommer et al., 2013; Jastreboff et al., 2013; Potenza et al., 2012). The stress imagery script was developed from a participant’s account of one of the most personally stressful events occurring in the past 12 months. Participants rated the stressfulness on a 10-point Likert scale with “1=not at all stressful” and “10=the most stress they experience in the past year.” Scripts were developed only for situations rated as an eight or above. Examples include situations such as interpersonal conflict with a family member, unemploymentrelated stress, and illness/death of a loved one. Situations containing severe trauma were not included. The neutral-relaxing script was developed from an individual's experience of neutral-relaxing situations, such as reading in bed at night, watching television, or reclining on a sofa.

fMRI Procedure and Acquisition

Approximately one hour prior to the scanning session, participants were guided on specific aspects of the study procedures and trained specifically in guided imagery and relaxation procedures as described previously (Elsey et al., 2015; Hommer et al., 2013; Jastreboff et al., 2013; Potenza et al., 2012).

The fMRI session consisted of participants being exposed to three imagery conditions: spiritual, stress, and neutral-relaxing. Two scripts of each type were developed (i.e., two spiritual, two stress, two neutral-relaxing); thus, each participant was exposed to a total of six scripts. Each script was recorded using the same female voice.

Only the stress condition was examined for the purpose of the current study, as only this condition was relevant to the aims of the study (i.e., to examine spirituality-specific neural correlates of stress-induced anxiety). For stress scripts, participants described particular situations in which they felt sad, mad, and upset and which could not be changed in the moment (e.g., relational conflict, termination at work). The severity of the situations were self-rated on a 10- point Likert scale (1=not at all stressful and 10=the most stressful). Only events rated as 8 or above were used for script development.

Magnetic resonance imaging data were collected using a 3-T Siemens Trio MRI system equipped with a standard quadrature head coil, using T2-sensitive gradient-recalled single-shot echo-planar pulse sequence. Anatomical images of the functional slice locations were acquired with spin-echo imaging in the axial plane parallel to the AC-PC line with TR=300 ms, TE=2.46 ms, bandwidth=310 Hz/pixel, FA=60°, field-of-view=220x220mm, matrix=256x256, 32 slices with slice thickness=4mm and no gap. Functional images were collected with a single-shot gradient echo-planar-imaging (EPI) sequence. Thirty-two axial slices parallel to the AC-PC line covering the whole brain were acquired with TR=2,000 ms, TE=25 ms, bandwidth=2003 Hz/pixel, FA=85°, field-of-view=220x220 mm, matrix=64x64, 32 slices with slice thickness=4mm and no gap. Then, a high-resolution 3D Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence (TR=2530 ms; TE=2.77 ms; bandwidth=179 Hz/pixel; FA=7°; slice thickness=1 mm; field-of-view=256x256 mm; matrix=256x256) was used to obtain sagittal images for multi-subject registration.

Six fMRI trials (two per condition) were acquired using a block design. To control for nonspecific order effects, condition order was randomly assigned and counterbalanced across participants. Each script was presented only once for each subject, and scripts in the same condition were not presented consecutively. Each trial lasted a total of five minutes, including a 1.5-minute quiet baseline period followed by 2.5-minute imagery (consisting of two minutes of read imagery and a half-minute of quiet imagery) and a one-minute quiet recovery. During baseline, participants were instructed to remain still in the scanner without engaging in any mental activity. Before and after each trial, anxiety and spirituality ratings were verbally elicited using a 10-point Likert scale (0=”not at all,” 10=”extremely high”).

fMRI Analysis

fMRI data were first converted from Digital Imaging and Communication in Medicine (DICOM) format to analyze format using XMedCon. To achieve steady-state equilibrium between radiofrequency pulsing and relaxation, the first ten images of each trial were discarded. Images were slice-time-corrected using a custom-designed MATLAB program. Motion correction was conducted using SPM8 for three translational and three rotational directions, removing trials with linear motion exceeding 1.5 mm and a rotation greater than 2°. The recovery period (one minute) was excluded from the data analysis to prevent carryover effects from the imagery period.

Individual-level analyses were conducted using a general linear model (GLM) on each voxel in the entire brain volume with a task specific regressor (2.5-minute imagery relative to a 1.5-minute baseline) using Yale BioImageSuite (www.bioimagesuite.org). To account for potential variability in baseline fMRI signal, drift correction was included in the general linear model. Specifically, drift regressors were used to remove the mean time course, linear trend, quadratic trend, and cubic trend for each run. Each trial was normalized against the immediate baseline period preceding the script and then the two trials of the same type were averaged. Functional images were spatially smoothed with a six-mm Gaussian kernel, resulting in normalized beta maps in the acquired space (3.44mm×3.44mm×4mm). To bring data into a common reference space, three registrations were calculated within BioImageSuite: a linear registration was computed from the individual functional image to the corresponding individual participant 2D anatomical image, a linear registration was computed from the 2D anatomical image to the individual participants' 3D structural image, and a non-linear registration was computed between the individual 3D image and a standard reference 3D image, the

Colin27 Brain. In order to bring the data into a common reference space, all three registrations were concatenated and applied as one registration to the normalized beta-maps.

The AFNI software package (http://afni.nimh.nih.gov/afni) was used for whole-brain random-effects analysis to investigate main effects of condition (neutral–relaxing, stress, spirituality). Given significant results, in order to examine the source of the main effects of condition, these results were further examined using BioImageSuite using two-tailed t-test maps. Family-wise-error (FWE) correction for multiple comparisons was employed using 3dClustSim from AFNI utilizing the autocorrelation function option and 10,000 iterations. Input smoothness for these simulations was estimated from the residuals of the t-tests.

In order to examine the relationship between brain activations during the stress condition and subjective ratings measured by the ISS, a whole-brain correlational analysis was conducted using BioImageSuite. Age, gender, and years of education were included as control variables. To best identify relevant neural correlates while being appropriately conservative, a threshold of $p<0.05$ was employed for the whole-brain correlations. Additionally, to correct for multiple comparisons, a cluster-wise control of family-wise errors at $p<0.05$ was used.

Subjective Responses

Participants were questioned on their affective states immediately after listening to each of their individualized scripts. Specifically, following the stress condition, they were asked "On a scale of 0-10, how anxious do you feel?" Participants also completed the Beck Anxiety Inventory (BAI), a 21-item scale which measures symptoms related to anxiety during the previous month (Beck et al., 1988). Each item is rated on a four-point scale on the degree to which anxiety-related symptoms, e.g. “unable to relax” or “fear of worst happening,” have been bothersome, with “3=Severely—it bothered me a lot” and “0=Not at all.” ISS scores were correlated with both in-scanner subjective anxiety scores and out-of-scanner BAI scores, while controlling for age, gender, and years of education. Exploratory correlational analyses were also conducted for ISS scores with subjective anxiety scores and BAI scores separately for women and men.

Results

Sample Description

Table 1 summarizes the demographic characteristics and ISS scores for the sample. Participants included 24 young adults between the ages of 18 and 27 years. No sociodemographic variable was significantly associated with ISS scores except for education ($r = -0.45$, $p < 0.05$).

Table 1. Participant demographic information

n	24
Male/Female	15/9
Age	22.2 (2.3)
White/Black/Asian/Other	15/5/3/1
Non-Hispanic/Hispanic	22/2
Years of education	15.0 (1.7)
Body mass index	22.4 (2.3)
ISS score	5.83 (3.0)

Mean values (SD) are denoted for age, education, body mass index, and ISS score.

Subjective Responses

Correlational analyses were conducted to examine the associations between intrinsic spirituality, as measured by the ISS, and in-scanner subjective anxiety ratings and out-of-scanner trait anxiety, as measured by the BAI. Neither self-reported anxiety ratings ($\beta = 0.15$, $p > 0.05$) nor BAI scores ($\beta = -0.25$, $p > 0.05$) were significantly associated with ISS scores during stress. Exploratory correlation analyses showed that ISS scores negatively correlated with BAI scores in men ($r = -0.53$, $p < 0.05$), but no significant correlation was found in women ($r = 0.25$, $p > 0.05$).

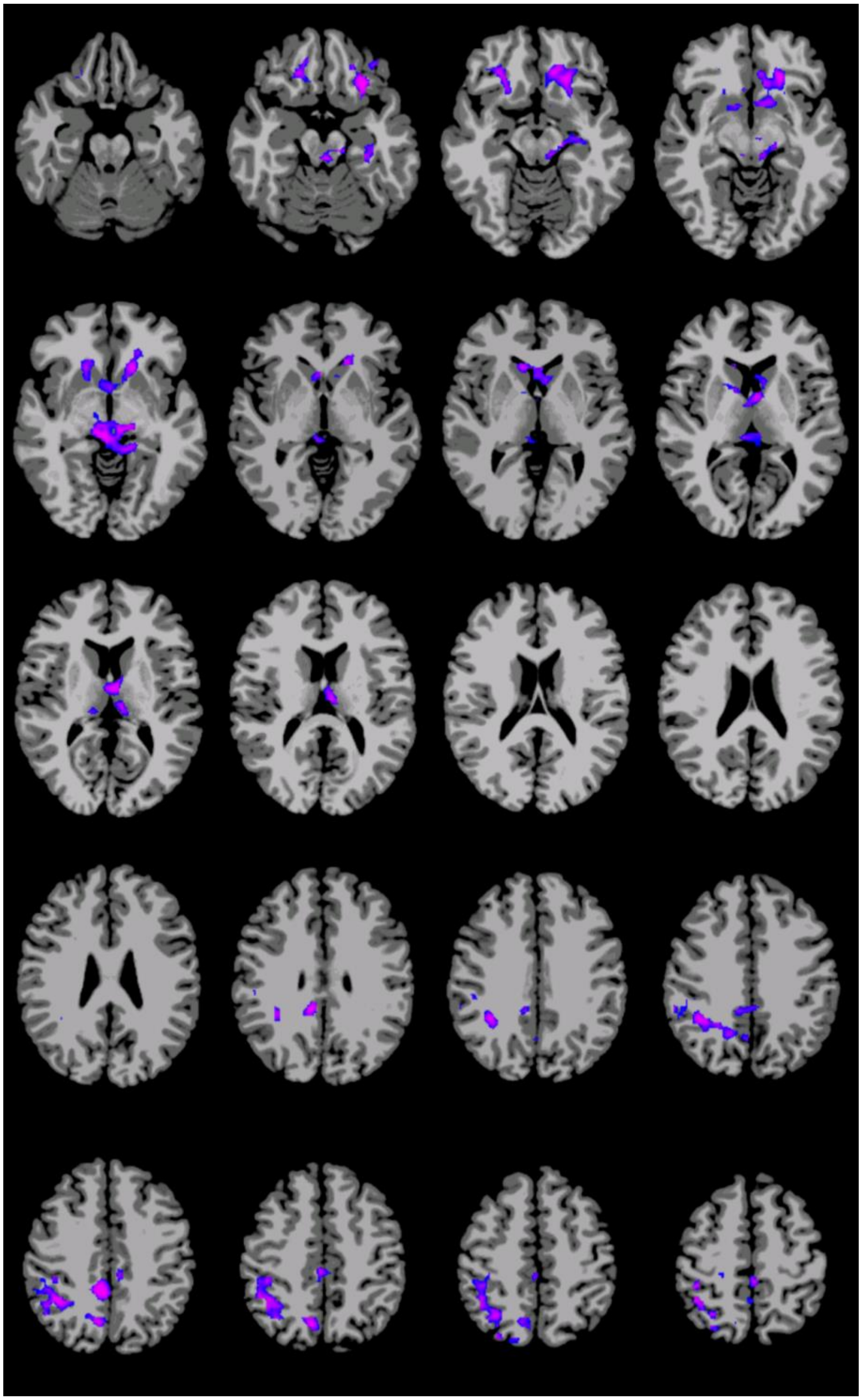
fMRI Correlations with Intrinsic Spirituality Scale (ISS)

Whole-brain correlation analyses during the stress condition relative to the neutral-relaxing condition indicate a correlation between ISS scores and reduced activity in a corticostriatal-limbic circuit that includes the hippocampus, brain stem, thalamus, ventral striatum, orbitofrontal and ventromedial prefrontal cortex (Table 2 and Figures 1 and 2; whole-brain corrected at $p < 0.05$). ISS scores correlated with reduced activity in another cluster that includes the posterior cingulate and right inferior parietal lobule (Table 2 and Figures 1 and 3; whole-brain corrected at $p < 0.05$). The scatter plots in Figures 2 and 3 illustrate negatively correlated patterns in these two clusters.

Table 2. Relationship between ISS scores and brain activity during the stress condition in N=24 participants.

Brain region	BA	Peak x	y	z	Volume (mm^3)	*k*	R-Value Max	Mean	SD
Brain Stem/Striatum/Prefrontal Cortex		-27	27	-15	12450	461	-0.76	-0.48	0.06
Brain stem					*1244*	*46*	*-0.63*	*-0.47*	*0.04*
Hippocampus					*272*	*10*	*-0.60*	*-0.48*	*0.05*
Ventral striatum					*2331*	*86*	*-0.65*	*-0.46*	*0.04*
Thalamus					*1436*	*53*	*-0.69*	*-0.50*	*0.06*
Orbitofrontal cortex	*11, 32*				*2192*	*81*	*-0.76*	*-0.51*	*0.07*
Ventromedial prefrontal cortex	*11, 47*				*1924*	*71*	*-0.74*	*-0.49*	*0.05*
Posterior Cingulate/Parietal Lobe		33	-60	63	10598	393	-0.76	-0.47	0.05
Right inferior parietal lobule	*7, 39,40*				*5540*	*205*	*-0.67*	*-0.47*	*0.05*
Posterior cingulate					*1923*	*71*	*-0.64*	*-0.48*	*0.05*

Figure 1. Whole-brain correlations between neural activity and ISS scores during the stress condition in N=24 participants.



Regions are those identified in whole-brain correlations (see Table 2). Blue color indicates areas where participants show relatively reduced activation. The right side of the brain is on the left.

Figure 2. Correlations between brain activity during the stress condition and subjective measures on the ISS in N=24 participants.

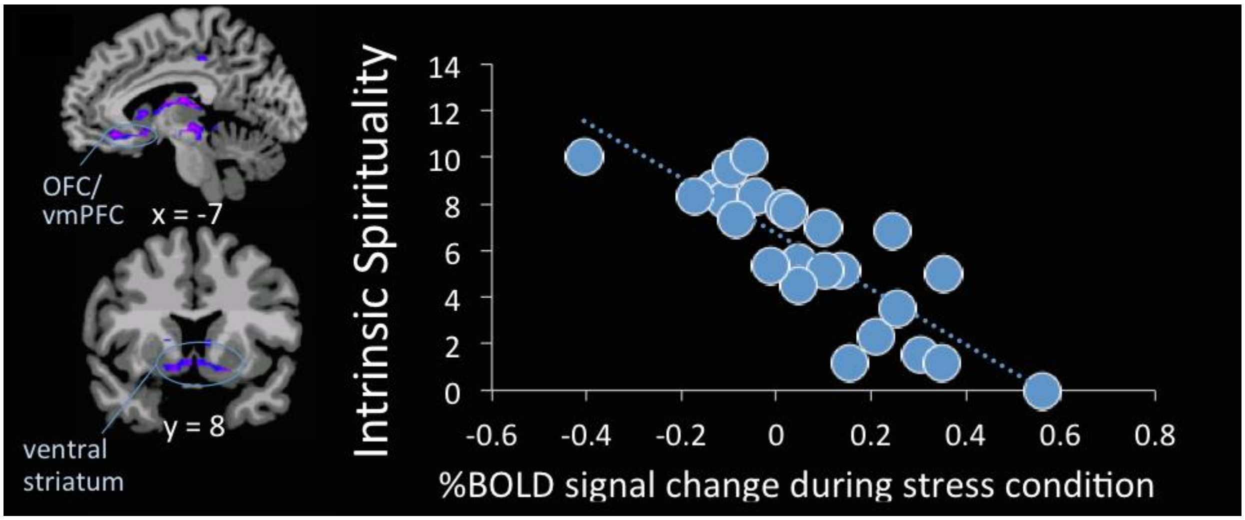


Figure demonstrates a negative correlation between activity in the orbitofrontal cortex (OFC),ventromedial prefrontal cortex (vmPFC) and ventral striatum during the stress condition and decreasing scores on the intrinsic spirituality scale. Scatterplot on the right depicts percent blood-oxygen-level-dependent (BOLD) signal change in these areas correlated with scores on the ISS.

Figure 3. Correlations between brain activity during the stress condition and subjective measures on the ISS in N=24 participants.

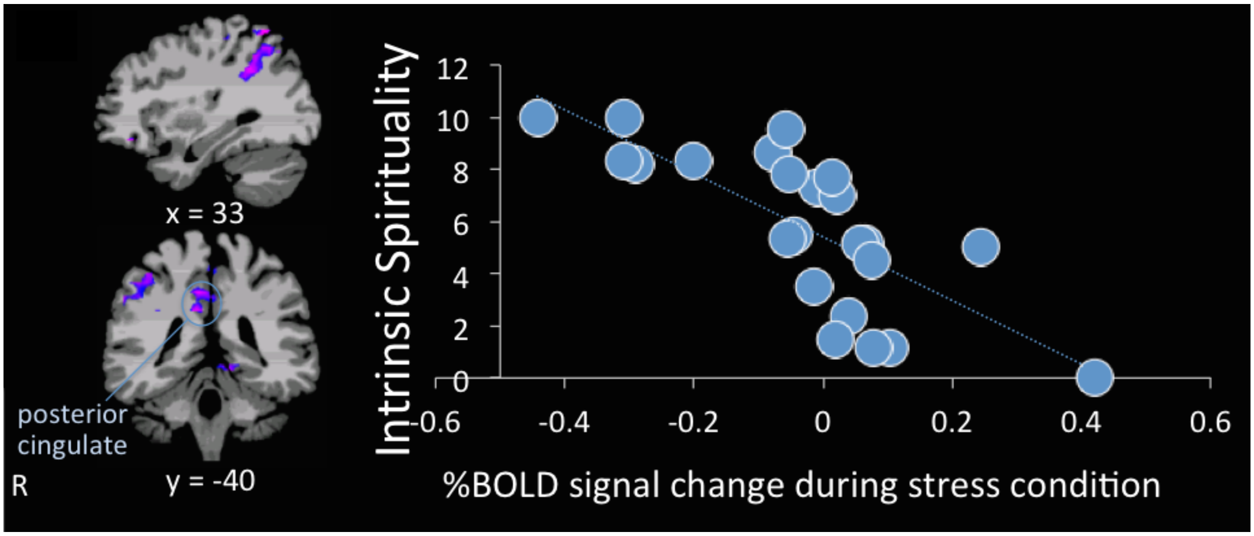


Figure demonstrates a negative correlation between activity in a posterior cingulate cluster during the stress condition and decreasing scores on the intrinsic spirituality scale. Scatterplot on the right depicts percent blood-oxygen-level-dependent (BOLD) signal change in this cluster correlated with scores on the ISS.

Discussion

The present findings demonstrate that during a stressful experience higher intrinsic spirituality is associated with greater deactivation in the hippocampus, brain stem, ventral striatum, and thalamus, extending to the orbitofrontal cortex (OFC) and ventromedial prefrontal cortex (vmPFC), as well as in another cluster comprising of the posterior cingulate cortex (PCC) and right inferior parietal lobule. These areas overlap with brain regions that are activated during a stress exposure and have been previously implicated in stress responsiveness, emotional and cognitive processing, and self-referential processing (Brewer et al., 2013; Li & Sinha, 2008; Van Oort et al., 2017). These novel findings demonstrate that intrinsically spiritual individuals evoke greater deactivation of brain regions involved with responsivity to stress. This is the first study to examine neural correlates of spirituality during a stress exposure. Given previous research showing a relationship between spiritual traits, states, and practices and perceived stress (Greeson et al., 2015; Southwick & Charney, 2012), the results provide a potential neural substrate for how spirituality may influence stress processing.

Stress Response in Striatal-Limbic Circuitry

Consistent with previous findings in which thalamic and striatal regions were activated during a stress exposure relative to a neutral condition but were deactivated during spiritual experience relative to stress (Miller et al., 2018), individuals with high intrinsic spirituality exhibited greater deactivation in the thalamus and ventral striatum. The thalamus relays sensory and emotional signals between various subcortical areas and the cerebral cortex (Sherman & Guillery, 2001). The striatum is implicated in the control of cognitive, emotional, and complex motor functions, all of which are modulated by stress (Balleine et al., 2007; Kelley, 1999).

Motivational and emotional stimuli influence neurons in the ventral striatum (Williams et al., 1993), which consists of the nucleus accumbens and olfactory tubercle. As part of a corticostriatal-limbic loop, the ventral striatum receives direct input from multiple regions such as the thalamus, amygdala, hippocampus, and brain stem and projects outputs primarily to the ventral pallidum and the medial dorsal nucleus of the thalamus, which then projects to the cortex (Haber & Behrens, 2014).

Other subcortical regions included in the cluster associated with intrinsic spirituality were the hippocampus and midbrain area of the brain stem. A mesolimbic pathway projects to the nucleus accumbens from midbrain regions like the substantia nigra and ventral tegmental area, which are densely populated with dopaminergic neurons (Kalivas, 1993; Williams et al., 1993). While midbrain dopamine neurons play central roles in reward processing, they also play a role in processing noxious stimuli, including psychological stress (Brischoux et al., 2009; Saal et al., 2003). The hippocampus, in addition to having a vital role in declarative memory, is a key regulator of the HPA axis and contains large numbers of glucocorticoid receptors, making it more vulnerable to long-term stress than most other areas of the brain (Bremner, 2007; Joëls, 2008). Stress and glucocorticoids have been shown to cause dendritic shrinkage and loss of spines in the hippocampus (McEwen et al., 2015), and a brief exposure to acute stress impairs hippocampal synaptic plasticity (Kim & Diamond, 2002; Shors et al., 1989; Yang et al., 2004).

A substantial body of research has demonstrated that a striatal-limbic circuit which includes the striatum, thalamus, midbrain, and hippocampus, as well as amygdala, hypothalamus, and insula, are involved in physiological and emotional responses to stress in healthy and patient populations (Seo et al., 2017; Seo et al., 2011; Seo et al., 2014; Sinha, 2008). Furthermore, higher levels of stress are associated with increased striatal-limbic level responding in both healthy and patient populations (Arnsten & Goldman-Rakic, 1998; Li & Sinha, 2008; Oswald et al., 2007; Potenza et al., 2012). Previous adversity and negative life events appears to further increase striatal-limbic sensitivity to acute emotional stress (Seo et al., 2014). Activation in these regions, therefore, not only reflects a neural response to stress but also may become more sensitized in individuals with a greater accumulation of chronic stress.

Striatal-Limbic Hyperactivity Can Result in Impairment

Evidence suggests that the continual stimulation of this striatal-limbic circuit due to chronic stress could result in the strengthening of primitive emotional responses (Arnsten et al., 2015; Seo et al., 2011). Research has shown, for example, that exposure to stress upregulates and eventually compromises striatal functioning (Rossi et al., 2008). Additionally, dopamine release in the ventral striatum during stress has been found to be related to early life parental care. More specifically, in individuals who received low parental care, stress caused a significant release of dopamine in the ventral striatum, suggesting that vulnerability to stress is related to exaggerated dopaminergic projections to the ventral striatum (Pruessner et al., 2004). Similarly, Krishnan and colleagues (2007) demonstrated in an animal experiment on mice in which susceptible, but not unsusceptible mice, exhibited a prolonged upregulation in the firing of dopamine neurons from the ventral tegmental area to the nucleus accumbens and concluded that different transcriptional programs in these regions accompany differing levels of vulnerability to stress exposure. Another study showed that stress resulted in both increased functional connectivity in a network of subcortical regions that include the thalamus, striatum, and hippocampus as well as structural atrophy in these regions (Magalhaes et al., 2018). Taken together, stress-induced striatal-limbic hyperactivation represents a vulnerability factor and over time could underlie the pathophysiology of stress-related mental disorders such as depression, addictions, and posttraumatic stress disorder.

Stress Response in Prefrontal Cortical Areas

In addition to subcortical regions, results from the current study demonstrated that individuals high in intrinsic spirituality exhibited greater deactivation in OFC and vmPFC. The PFC receives visual, auditory, and somatosensory inputs and underlies a wide variety of cognitive and emotional functions (Van Der Werff et al., 2013). The OFC and vmPFC receive input largely from the dorsomedial thalamus and have anatomical connections with other regions including the ventral striatum, amygdala, hypothalamus, and hippocampus. The OFC and vmPFC are involved in cognitive and executive control functions such as inhibiting impulses, regulating emotion, focusing and shifting attention, monitoring behavior, representing reward, and making decisions (Arnsten, 1998; Milad & Rauch, 2007; Roberts et al., 1998).

Neuroimaging studies have shown that chronic stress is linked with mPFC function and structure (Lucassen et al., 2014). Maltreated children were found to have volume reductions in the OFC and middle temporal gyrus (De Brito et al., 2013). MDD patients with a history of childhood maltreatment demonstrated reduced functional connectivity within corticostriatal-limbic circuitry, which were associated with childhood neglect (Wang et al., 2014). Imaging studies in patients with stress-related affective and emotional disorders including major depressive disorder and post-traumatic stress disorder have also shown alterations in PFC volume (Pruessner et al., 2010; Sousa & Almeida, 2012).

In response to stress inductions through script-driven imagery, researchers have found widespread corticostriatal-limbic activations that include in medial prefrontal regions. Among healthy individuals, medial and lateral OFC and ventral PFC regions have consistently been identified as part of a stress-related circuit (Seo et al., 2017; Seo et al., 2011; Seo et al., 2019; Sinha, 2008). These regions were also activated during alcohol craving in social drinkers (Seo et al., 2011). Whole-brain correlational analyses have demonstrated associations between cumulative life adversity and increased prefrontal cortical activity during a stress induction (Seo et al., 2014). In a study on patients with cocaine use disorder, women exhibited activation in the ventral and dorsal PFC during stress, relative to neutral and craving experiences (Potenza et al., 2012).

Even mild stressors alter the morphology of the prefrontal cortex and can severely perturb prefrontal functions by altering dendritic organization in mPFC pyramidal neurons (Arnsten, 2009; Brown et al., 2005). Chronic stress causes neurons in the mPFC to develop dendritic debranching and shrinkage, which is associated with cognitive rigidity, while neurons in the OFC expand dendrites, which may be related to hypervigilance (Du et al., 2009; Karatsoreos & McEwen, 2011). Research also indicates that stress disrupts catecholamine modulation in prefrontal regions, which consequently impairs executive functions like self-control and working memory (Arnsten, 1998; Arnsten & Goldman-Rakic, 1998; Muraven & Baumeister, 2000).

Stress Response in the PCC and Inferior Parietal Lobule

Current findings also indicate that individuals high in intrinsic spirituality exhibit greater deactivation in the PCC and inferior parietal lobule. As one of the most metabolically active and highly connected regions in the brain, the PCC is involved in diverse functions, including internally directed thought, memory recollection, and regulation of attention (Leech & Sharp, 2013). The inferior parietal lobule has been implicated in self-representation in three-dimensional space (Assmus et al., 2003; Bolger et al., 2014). These two regions also form central nodes of the DMN of the brain, along with the precuneus and mPFC. The DMN deactivates during tasks that are directed externally or involve present-centered attention. Conversely, the DMN is activated when attention is internally directed in a self-referential way, like during episodic memory retrieval, self-evaluation, and daydreaming (Brewer et al., 2013; Brewer et al., 2011; Garrison et al., 2013; Leech & Sharp, 2013).

Though the DMN is not typically associated with the stress response, neuroimaging studies on stress, in fact, have consistently shown that stress exposure increases activity within the DMN (Dedovic et al., 2014; Fechir et al., 2010; Seo et al., 2011; Seo et al., 2014). Increased DMN functional connectivity has also been shown directly after a stress induction (Vaisvaser et al., 2013). One of the first studies to employ a stress-related guided imagery paradigm found that emotional distress was related to activation in the mPFC and PCC, as well as the ACC, striatum, thalamus, and hippocampus (Sinha et al., 2004). Other guided imagery studies have similarly found increased DMN-related activations in the mPFC, PCC, precuneus, and inferior parietal lobule during stress exposures (Seo et al., 2017; Seo et al., 2011; Seo et al., 2019).

Potential Role of the DMN During Stress Response

The increase in self-referential processing that often co-occurs with a stressful event may be related to increased DMN activation (Van Oort et al., 2017). Unlike some experimental procedures that induce stress in a non-individualized manner and in a way which does not involve self-focus, like mental exhaustion tasks or physical discomfort (Quaedflieg et al., 2013; Tanosoto et al., 2012), guided imagery stress inductions explicitly elicit situations of high emotional distress particular to an individual's own history (Sinha, 2009). Thus, studies that utilize this paradigm, including the current investigation, elicit a personally salient stressful experience in which mental and emotional self-involvement is a salient feature. Research that examined social rejection, similarly, observed that emotional stress was related to increased DMN activity (Muscatell et al., 2015). Results of the present study suggest that individuals high in intrinsic spirituality experience less self-focus during experiences which involve considerable mental and emotional self-involvement.

DMN activity is also relevant to mental health and resilience. Depressed patients have shown deficits in deactivation of the DMN during various tasks (Hamilton et al., 2011). On the other hand, deactivations of the DMN mediate both experiential decentering and decreases in depressive symptoms and risk of relapse (Bieling et al., 2012; Heeren & Philippot, 2011). Studies have also found that other clinical and sub-clinical symptom reductions in other disorders, including social anxiety and attention deficits, are associated with reduction of DMN activity (Farb et al., 2007; Froeliger et al., 2012; Goldin et al., 2009; Paul et al., 2012).

Spirituality and Mindfulness Associated with DMN Activity

The current findings of DMN deactivation in individuals higher in intrinsic spirituality during a stress response is consistent with research broadly on contemplative and spiritual traits and practices. A review of studies on spiritual beliefs and practices found that a relative reduction in parietal cortex activation, particularly in the inferior parietal cortex, is reflective of spiritual belief both within and without a context of meditative practice (Barnby et al., 2015). A study of individuals at high and low familial risk for depression showed that greater personal importance of religion or spirituality in high risk individuals was associated with decreased DMN connectivity (Svob et al., 2016). Deactivation in the middle and posterior cingulate and parietal cortices were part of a functional network involved in personally meaningful spiritual experiences, suggestive of a reduction in self-focus and a less bounded, more expanded sense of self during such experiences (McClintock et al., Manuscript submitted for publication). The practice of mindfulness meditation has been shown to have a similar decentering effect (Holzel et al., 2011; Vago & Zeidan, 2016), and research indicates that reduction in default mode processing may represent a central neural process in long-term practitioners of meditation (Berkovich-Ohana et al., 2014; Garrison et al., 2015). In an investigation of multiple types of meditative exercises, primary nodes in the DMN were deactivated in experienced meditators across meditation types (Brewer et al., 2011). Another study found that long-term meditators relative to novice meditators demonstrated less activity in the PCC during both meditation and at rest (Panda et al., 2016). Similar to findings on DMN functional connectivity in individuals who place high personal importance in religion or spirituality (Svob et al., 2016), experienced meditators compared to beginners have also exhibited weaker functional connectivity between DMN regions (Lutz et al., 2016; Taylor et al., 2013).

Research indicates, therefore, that decreased activation and functional connectivity in the DMN represents a neural substrate shared by both experienced meditators and intrinsically spiritual individuals. Considered conceptually, a spiritual orientation to life and the cultivation of one’s spirituality through contemplative practice go hand in hand, as individuals who are intrinsically motivated by spirituality would be more likely to engage in regular spiritual practice, and vice-versa (Walsh & Shapiro, 2006). These groups share a commitment—in motivation, intention, and behavior—to a focus of attention and awareness beyond oneself and towards a self-transcendent, numinous level of awareness and reality. Supporting this notion, research has shown a high degree of correlation between an intrinsic commitment to spirituality and contemplative practice (McClintock et al., 2016).

Intrinsic Spirituality and Anxiety

In the current data, no association was found between intrinsic spirituality and in-scanner anxiety ratings. These results suggest that, despite greater deactivation in stress-related brain regions, intrinsic spirituality may be independent of the subjective perception of anxiety during a stress exposure. Consistent with these findings, studies of experienced meditators during physical or emotional distress have reported differences compared to controls in neural response and unpleasantness but no differences in perceived intensity of distress (Gard et al., 2012; Lutz et al., 2013). Brain deactivations may implicate perceptual and mental processes relevant to the stress response, like intrusive memories or negative cognitions, which are implicated in associated brain areas like the mPFC and hippocampus (Anderson & Levy, 2009; Benoit et al., 2015). Taken together, spiritual commitment and practice may influence neural processes and the way in which one relates to distress but not the subjective perception of distress itself.

Possibly qualifying this interpretation, current data also showed an association between higher intrinsic spirituality and lower levels of out-of-scanner trait anxiety in men but not in women. Previous research indicates gender differences in trait anxiety, such that women exhibit higher levels of overall anxiety and greater prevalence of disorders like panic disorder, generalized anxiety disorder, and post-traumatic stress disorder (Mclean & Anderson, 2009), and neuroimaging studies have shown that women and men recruit different neural resources during stress-induced anxiety (Seo et al., 2017; Seo et al., 2011). Given the gender disparity, it is possible that intrinsic spirituality has an influence on anxiety in men, but not women, because of differences in susceptibility to anxiety. However, other interpretations including the link between anxiety and negative emotional bias are possible (Watson et al., 1988), and future research to further delineate the relationship between spirituality, stress processing, subjective anxiety, and gender is warranted.

Implications and Future Directions

A potentially alternative emotion regulatory pathway. Emotion regulation refers to altering the nature, intensity, and duration of emotional responses through regulatory processes (Ochsner & Gross, 2005). Substantial research has been conducted on emotion regulatory strategies that involve the control of emotion primarily through cognitive means, utilizing voluntary methods like suppression of emotional expression and cognitive reappraisal (Ochsner et al., 2012). Neuroimaging studies have shown that these explicit strategies are mediated by increased activation in prefrontal cortical regions as well as in the ACC, which leads to greater response inhibition and down-regulation of subcortical regions like the amygdala (Ochsner & Gross, 2005). Despite receiving less neuroscientific attention, other emotion regulation strategies have demonstrated efficacy including those that are more implicit, automatic, and bottom-up (Chambers et al., 2009; Williams et al., 2009). While future studies are warranted, the present results suggest an emotion regulatory pathway that involves a decrease rather than an increase in prefrontal cortical activation, as well as decreased activation in posterior nodes of the DMN.

Decreased prefrontal activation suggests a reduction in top-down cognitive control, which is consistent with research on experienced Buddhist meditators during physical and emotionally aversive experiences. In a study of long-term mindfulness practitioners who received an electric shock, practitioners compared to non-practitioners experienced less unpleasantness and exhibited decreased prefrontal cortical activation (Gard et al., 2012). Similarly, Zen practitioners who experienced thermal pain exhibited reduced activation relative to non-practitioners in the PFC, as well as amygdala and hippocampus (Grant et al., 2011). Years of experience with Zen, furthermore, correlated with greater deactivation.

Consistent with cognitive regulatory strategies like reappraisal, however, some studies have shown that meditation influences brain activity involved in regulating distress, such that prefrontal regions display greater activation in response to aversive stimuli (Allen et al., 2012; Hölzel et al., 2013; Zeidan et al., 2014). A study that compared experienced meditators with novice meditators in viewing emotionally evocative pictures yields insight into differential findings. While viewing pictures in a mindful state, experienced meditators exhibited greater deactivation in prefrontal cortical areas but no changes in subcortical regions involved in emotional processing, while novice meditators exhibited increased prefrontal activations with simultaneous down-regulation of the amygdala (Taylor et al., 2011). A separate study found that higher trait mindfulness was associated with reduced prefrontal activations when viewing emotionally provoking pictures (Lutz et al., 2014). These findings suggest that individuals with little or no experience in contemplative or spiritual practice may recruit prefrontal regions to down-regulate subcortical affective neural regions, while long-term practitioners may approach emotional stimuli with a greater acceptance of distressing emotional states and enhanced present-moment awareness.

Differences between deliberate cognitive regulatory strategies and a more bottom-up, implicit process that may occur in intrinsically spiritual individuals parallel contrasting methods of modifying emotion within the cognitive-behavioral therapy literature, specifically the different approaches that underlie cognitive restructuring and cognitive defusion (Deacon et al., 2011). While interventions that utilize cognitive restructuring seek to alter the content of mental and emotional experiences and are largely antecedent-focused, interventions that involve cognitive defusion, including Acceptance and Commitment Therapy and Dialectical Behavior Therapy, alter one’s relationship to stress-provoking events and are thus response-focused. The key difference with cognitive defusion lies in learning to accept one's inner experience, rather than reflexively focusing on and modifying cognitions (Chambers et al., 2009).

Greater deactivation in the DMN suggests that intrinsically spiritual individuals may experience less self-involvement and identification with mental and emotional stimuli during stress exposures. A more subjectively spacious and diffuse sense of self, which is typically reported during spiritual experiences (Hood, 1975; James, 1902; Newberg & Newberg, 2006), may be essential to the capacity to accept and tolerate emotional distress. This notion is supported by a study that showed that dispositional mindfulness during noxious thermal stimulation was associated with lower pain intensity and unpleasantness ratings and greater deactivation of the precuneus and PCC (Zeidan et al., 2018). Research indicates that PCC-related activation corresponds with a greater propensity to personalize distressing events, suggesting that individuals higher in trait mindfulness or spirituality may have a greater ability to gain greater experiential distance from, and therefore higher tolerance of, aversive stimuli (Andrews-Hanna et al., 2010; Kim & Johnson, 2013; Zeidan & Vago, 2016). Intrinsically spiritual individuals tend to trust in a higher purpose and intelligence even during ostensibly adverse circumstances (Pargament et al., 1998; Zinnbauer et al., 1997), which may also lead to greater acceptance of such situations and to less rumination, chronic worry, and other maladaptive forms of coping. Beyond the similarities in neural activation, both intrinsic spirituality and dispositional mindfulness involve decentering one's awareness beyond an individual sense of self and accepting rather than resisting one's experience regardless of perceived valence or utility.

Clinical implications. The present study yields information relevant to understanding factors and mechanisms that promote rapid recovery during acutely stressful and adverse situations and that could inform clinical interventions for patients with stress-related mental disorders. Though the sample in the present study consists of healthy participants, evidence exists that neural mechanisms involved in adaptive stress responses also comprise targets of stress exposure in the development of maladaptive states, particularly when neural activation becomes excessive and prolonged (Balodis & Potenza, 2015; Krishnan et al., 2007; Mulders et al., 2015; Radley et al., 2015). According to a stress-vulnerability view of mental disorders, psychopathology develops from the interaction of stressors and specific vulnerabilities in an individual (Faravelli et al., 2012). For example, increased dopamine release in the nucleus accumbens in the context of a psychosocial stressor may promote alertness necessary for survival during potentially dangerous situations, yet neuroplastic changes in this circuitry over time may also lead to overgeneralization. This neural circuitry has, in fact, been implicated in disorders like substance use disorders and post-traumatic stress disorder (Arnsten et al., 2015; Balodis & Potenza, 2015; Krishnan et al., 2007). Other disorders, including depression and anxiety disorders, also share neural mechanisms with the response to acute stress during health, including hyperactivation and hyperconnectivity in the DMN (Grimm et al., 2009; Segal et al., 2006; Stein et al., 2002). Thus, studying neural mechanisms that mediate the response to severe stress can provide valuable insight into how to promote human resilience and to improve treatment of stress-related disorders.

Research also shows that dysregulation resulting from multiple stressors leads to allostatic load and, that, furthermore, cumulative adversity is associated with worse mental health outcomes (McEwen, 1998; Seo et al., 2014). Cumulative adversity is also related to greater activation in stress-related circuits during a stress induction as well as structural atrophy in brain regions such as the hippocampus, brain stem, striatum, ACC, and PFC (Ansell et al., 2012; Frodl & O'keane, 2013; Magalhaes et al., 2018). Factors that attenuate underlying neural mechanisms of the stress response, therefore, may reduce the cumulative effects of chronic stress. Likewise, developing interventions that can reduce behavioral and biological sequelae of psychological stress would have critical importance for prevention and treatment (Cohen et al., 2007). Identifying imaging markers that detect susceptibility and resilience to adverse effects of stress would also facilitate clinical practice and allow earlier and more targeted interventions (Savitz et al., 2013). The current findings suggest that spirituality may be related to better mental health outcomes, in part, because of deactivations in brain regions involved with acute stress response. The following sections will discuss in greater detail possible implications for the treatment and prevention of two categories of stress-related mental disorders in particular, substance use disorders and depressive disorders.

Implications for substance use disorders. Considerable evidence from population-based and clinical studies indicates that psychosocial adversity and stress is associated with greater vulnerability to addiction across substances and throughout the addiction process, from initiation to maintenance and withdrawal phases (Becker, 2017; Kreek & Koob, 1998; Sinha, 2008). Controlled experiments have shown that psychological stress induces strong drug cravings in substance disordered individuals (Andersen & Teicher, 2009; Sinha et al., 1999). Early life stressful events have been shown to correlate with severity of substance use disorder (Enoch et al., 2010; Khoury et al., 2010), and research indicates a dose-dependent relationship between accumulated lifetime adversity and risk of addiction (Sinha, 2008). Stress has also been identified as a key factor leading to drug relapse (Kreek & Koob, 1998; Sinha et al., 2006). Exposure to a variety of stressors has also been shown to reinstate previously extinguished cravings for substances including alcohol (Le et al., 2000; Le et al., 1998), nicotine (Buczek et al., 1999), heroin (Shaham et al., 2000; Shaham & Stewart, 1995), and cocaine (Ahmed & Koob, 1997; Erb et al., 1996).

Research indicates that a mesolimbic dopamine pathway which includes the striatum, midbrain, hippocampus, and amygdala is a key circuit that mediates the experience and regulation of both stress and addiction (Potenza et al., 2012; Swendsen et al., 2010). Moreover, dopamine accumulation in the ventral striatum is related to both stress-related and substance-related increases in cortisol (Oswald et al., 2005; Wand et al., 2007). Mesolimbic hyperactivation, in turn, leads to morphological changes in the mPFC, which affects a host of functions including impulse control, working memory, and decision-making (Arnsten, 1998; Arnsten & Li, 2005; Muraven & Baumeister, 2000). Since stress plays a significant role in initiating and maintaining substance use and abuse and is also a major impediment to successful rehabilitation, practices and interventions that aid stress management are essential to the prevention and treatment of substance use disorders. Moreover, because striatal-limbic activity increases during both acute stress and substance-related cravings, interventions that attenuate the hyperresponsiveness of this neural circuit would also be critical. Given the reduced activations associated with intrinsic spirituality in overlapping striatal-limbic circuitry, spirituality may represent a vital and clinically-efficacious component of interventions for substance use disorders.

Implications for depressive disorders. A considerable body of research has also found a strong link between exposure to stressful life events and depressive disorders (Kessler, 1997). The increased risk for depression may be a consequence of increased allostatic load, and depression may occur when an individual’s adaptive capacity falls short of allostatic demands (McEwen & Stellar, 1993). While much research has focused on stressful life events as triggers for the onset of depression, cumulative exposure to a variety of types of stressors, from childhood mistreatment to daily hassles, also contributes to symptoms of depression in adulthood (Vinkers et al., 2014). Additionally, increased stress predicts the clinical course of major depressive disorder, including longer duration, exacerbation of symptoms, worse treatment outcomes, and increased risk of future relapse (Hammen, 2005; Mazure, 1998).

Research also indicates that increased activation and functional connectivity in the DMN is associated with depressive disorders. The DMN is involved in a broad range of internal mentation (Buckner et al., 2008; Callard & Margulies, 2014). Rumination in particular has been shown to be associated with increased DMN activity (Burkhouse et al., 2017; Hamilton et al., 2011), and reductions in depressive symptoms are mediated by reduced rumination (Heeren & Philippot, 2011). Research has shown that depressed patients relative to healthy individuals exhibit increased and more sustained DMN activation when viewing emotionally provocative pictures, indicating deficits in deactivation of DMN in individuals with depression (Grimm et al., 2009; Sheline et al., 2009). Furthermore, the duration of DMN activity during these tasks were associated with symptom severity (Grimm et al., 2009). Depression and related symptoms of rumination and brooding are associated with increased functional connectivity between nodes of the DMN and the subgenual anterior cingulate (Berman et al., 2014; Berman et al., 2010; Greicius et al., 2007), a region implicated in the processing of sadness, fear, and stress (Mayberg, 1997; Phan et al., 2002).

Because DMN activity increases during both acute stress exposure and ruminative activity and is associated with depression, interventions that attenuate the hyperactivation and hyperconnectivity of this neural circuit would be critical in the treatment and prevention of depressive disorders. Given the reduced activations during stress associated with intrinsic spirituality in overlapping DMN circuitry, interventions for depression that include a component of spirituality may improve clinical outcomes. This claim is further supported by previous spirituality research that demonstrates both associated reduction in depressive symptoms and reduced DMN activation and functional connectivity (Brewer et al., 2011; Kasen et al., 2012; McClintock et al., 2016; Svob et al., 2016).

Integrating spirituality into psychological interventions. With over 100,000 groups worldwide represented in nearly every country, Alcoholics Anonymous is a widespread and an unapologetically spiritual program for individuals who seek to achieve sobriety (BBC, 2015; Kaskutas et al., 2003). Involvement with Alcoholics Anonymous and similar twelve-step programs like Narcotics Anonymous have been found in many studies to be associated with abstinence from alcohol and other substances (Fiorentine, 1999; Kaskutas, 2009). Furthermore, spiritual changes like increased spiritual experiences and cultivation of qualities like forgiveness and humility have been associated with sustained sobriety over the course of recovery (Kelly et al., 2011; Robinson et al., 2011). Outcomes of these twelve-step facilitation therapies are as good or better than other substance use disorder treatments like cognitive-behavior therapy and motivational enhancement therapy (Fuller & Hiller-Sturmhofel, 1999). Other interventions have begun to include transcendental and mindfulness meditations, and research has linked these to lower risk for substance use, depression, and related clinical issues (Dakwar & Levin, 2009; Nidich et al., 2018). Similarly, studies on therapies for depression that have included elements of spirituality and mindfulness like religiously-integrated cognitive behavioral therapy (RCBT) and mindfulness-based cognitive therapy (MBCT) have been shown to be as effective, if not more so, than convention treatments (Koenig et al., 2015; Kuyken et al., 2008; Teasdale et al., 2000). For

MBCT patients, the decentering experience in particular has been associated with reductions in risk for relapse (Bieling et al., 2012).

Nevertheless, further possibilities exist for the integration of spirituality into interventions for substance use disorders, depression, and other stress-related mental illnesses. Although contemplative research has tended to focus on mindfulness meditation, contemplative spiritual practices in fact include wide-ranging techniques, from sitting practices like centering prayer and kundalini meditation to movement-based practices like qigong and yoga, and from ritual and chanting to engaging with sacred texts (Walsh & Shapiro, 2006; Wilber et al., 2008). For those patients who already are spiritually oriented and/or religiously affiliated, providing encouragement and guidance to engage in some of these traditional practices, perhaps with the assistance of a chaplain or in the context of their religious or spiritual community, may appropriately supplement conventional psychological and pharmacological treatments. Moreover, as research has shown a link between blaming or rejecting God and worse clinical outcomes (Pargament et al., 1998; Van Dyke et al., 2009), encouragement to not "give up on God" despite current adversities may be clinically indicated. Including additional components of spirituality and conducting research on their mechanisms and outcomes may lead to novel interventions and improved efficacy.

For individuals who are not spiritually inclined, a number of contemplative practices—such as transcendental meditation, lectio divina, and taijiquan—have been distilled in more ecumenical and secularized forms (Nidich et al., 2018; Wang et al., 2010). It is also possible that certain cognitive capacities that are related to spirituality without being explicitly spiritual could have clinical relevance. For example, one may learn to accept rather than resist one's inner experience of the moment, regardless of its apparent valence, without explicitly surrendering to a higher power or transcendent reality. Also implied in the spiritual life is a focus of attention beyond self-related mental activity. While traditional spiritual practices may deliberately train various types of self-transcendent awareness, secular meditations and other attention-regulating practices may serve similar functions that interrupt habitual self-focus and ruminative thought processes. Spirituality involves an expansive perspective on life, but adopting larger perspectives through other means like literature, philosophy, or simply an interest in world events may have a similar decentering influence during times of acute distress. In the psychodynamic literature, providing a protective holding environment for the patient is seen as crucial for increasing tolerance of uncomfortable affective states and allowing fundamental shifts to take place in the therapeutic process (Mitchell & Black, 2016). Similarly, secure attachment relationships have been linked with greater emotion regulation (Cooper et al., 1998). Thus, attachment relationships to therapists may function similarly to a relationship with a spiritual higher power in this regard.

In addition, given a potential emotion regulatory pathway that involves DMN deactivation, tools in applied neuroscience might also be developed to help regulate emotionally aversive experiences and reduce the cumulative effects of chronic stress. Real-time fMRI and/or functional near-infrared spectroscopy (fNIRS) neurofeedback could be used to systematically train DMN and other neural circuits involved in the regulation of stress. A number of neurofeedback studies have already shown encouraging results for targeted neuromodulation (Barth et al., 2016; Lawrence et al., 2014; Zotev et al., 2013), and future studies will be needed to refine this type of intervention for treating stress-related disorders and enhancing resilience to stress. Similarly, repetitive transmagnetic stimulation (rTMS) as well as pharmacological treatments that target reduction in DMN activity could be explored. Overall, evidence from the current study as well as previous research suggest that a number of elements directly or indirectly related to spiritual traditions might be effectively integrated into interventions and adjunctive treatments for stress-related disorders in order to sharpen adaptive and regulatory responses to stress.

Conclusion

The current findings provide a potential neural substrate associated with intrinsic spirituality during exposure to acute stress, suggesting a possible neural mechanism by which spirituality may buffer deleterious effects of stress. While the results may have mental health implications, future research is warranted. It is important to note that our sample is derived from a community population in which none met criteria for a current mental disorder and, therefore, the observed stress response is presumed to be healthy and adaptive. Evidence suggests, however, that adaptive and controllable responses to stress share highly overlapping neural circuits with maladaptive responses and, moreover, that cumulative life stress and adversity is associated with higher levels of psychopathology. Nevertheless, future studies on spirituality that recruit from clinical populations and which employ longitudinal designs would produce further insights about relationships between spirituality and stress. The current study did not include whole-brain correlations with intrinsic spirituality during the neutral condition, analyses of which would provide useful insight into whether the identified neural circuits are also associated with intrinsic spirituality in more normal moments of everyday life, or only under acutely distressing circumstances. Additionally, given the relatively small sample of participants, larger sample sizes would increase statistical power to detect hemodynamic signal and self-reported changes in anxiety and other subjective responses. Including other relevant neurobiological measures like cortisol levels, heart rate variability, and brain structure, too, would yield useful data for understanding how spirituality might influence the stress response.

Overall, the current findings advance knowledge about how spirituality is related to brain activity during exposure to stress. Future research can further delineate neural mechanisms that underlie the largely ameliorative relationship between spirituality and mental health and well-being. The widespread practice of spirituality in a multiplicity of forms across the globe lends real-life relevance to this line of research. It also has the potential to be translated into novel neuroscience-informed preventative and clinical interventions for individuals as well as communities. The rapid development of applied neuroscience tools like fNIRS, rTMS, and real-time fMRI neurofeedback could accelerate our understanding and application of this valuable knowledge. Overall, given the global prevalence of stress and related mental disorders, both need and opportunity exist to explore further the ways in which spirituality can promote greater resilience and well-being, and brain mechanisms that underlie these processes.

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Appendices

Appendix A: Intrinsic Spirituality Scale (ISS)

For the following six questions, *spirituality* is defined as one's relationship to God, or whatever you perceive to be Ultimate Transcendence.

The questions use a sentence completion format to measure various attributes associated with spirituality. An incomplete sentence fragment is provided, followed directly below by two phrases that are linked to a scale ranging from 0 to 10. The phrases, which complete the sentence fragment, anchor each end of the scale. The 0 to 10 range provides you with a continuum on which to reply, with 0 corresponding to absence or zero amount of the attribute, while 10 corresponds to the maximum amount of the attribute. In other words, the end points represent extreme values, while five corresponds to a medium, or moderate, amount of the attribute. Please circle the *number* along the continuum that best reflects your initial feeling.

1. In terms of the questions I have about life, my spirituality answers

no questions										**absolutely all my questions**
0	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	***10***

2. Growing spiritually is

more important than anything else in my life										**of no importance to me**
10	*9*	*8*	*7*	*6*	*5*	*4*	*3*	*2*	*1*	***0***

3. When I am faced with an important decision, my spirituality

plays absolutely no role										**is always the overriding consideration**
0	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	***10***

4. Spirituality is

the master motive of my life, directing every other aspect of my life										**not part of my life**
10	*9*	*8*	*7*	*6*	*5*	*4*	*3*	*2*	*1*	***0***

5. When I think of the things that help me to grow and mature as a person, my spirituality

has no effect on my personal growth										**is absolutely the most important factor in my personal growth**
0	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	***10***

6. My spiritual beliefs affect

absolutely every aspect of my life										**no aspect of my life**
10	*9*	*8*	*7*	*6*	*5*	*4*	*3*	*2*	*1*	***0***

Appendix B: Sample Personalized Scripts for the Stress Condition

Below are personalized scripts for the stress condition. Specifically, scripts from participants with the two lowest and the two highest ISS scores are listed below, for a total of eight sample scripts.

Participant 1: Low Intrinsic Spirituality (ISS = 0)

Stress Script 1

It's 11am on a rainy Thursday in August. It's Nancy's birthday today. You are in the Dodge Durango on your way to New Haven to get the keys for the new apartment. Your heartbeat quickens. KB uses the GPS to look up the route and starts to give you directions on the smaller highways. "I'd rather be on the 95, let's take that route, even if it's longer," you say. You grip the steering wheel tightly and take the next exit to get off the highway. You tense the muscles in your back and arms. You're driving fast as you try to get off the interstate. Your heart beats faster. The highway ends quickly and you have to make the first immediate right. You clench your jaw. You try to make the turn, but the car has poor adjustment. You are breathing faster now. You can feel that the wheels aren't responding fast enough. Your thoughts are racing. You know you need to hit the brakes a bit, but not too much. Your heart is pounding in your chest. You have no more control now; the car is swerving into the 6 lane highway. Your whole body is tense. You know you're going to hit something now. You tense all the muscles in your body. You hear the crunching metal as the car hits a pole and it immediately disappears. It's hard to breathe. You try to turn the car more and merge onto the other highway, but it's no use. You hear hard metal crunching again as you slam into the blue car in the intersection. You are tense all over. You see how the car hoods merge and the airbags explode in the other car. The car is finally stopped. There's a heavy weight on your chest. You put the car in park. You take your hands off the wheel. Your hands won't stop shaking. You know you could've avoided all this if you'd just slowed down. It's completely your fault. There is a deep intense pain sensation in your body. Tears come to your eyes.

Stress Script 2

It's 11am on July 1st . You are giving your SRT talk today. Your heart is beating faster. You are sitting on your bed at home reviewing your talk and practicing it out loud. You tense the muscles in your face and forehead. You feel like you're running out of time. Your breathing is shallow, and it feels hard to take a deep breath in. You try to remember the comments people made in the lab during the practice talk. You feel restless. This is the first time everyone in the department will hear what you're doing. There's a heavy feeling in your stomach. You know the evaluators won't be imagers, so you need to be able to defend the validity of your methods. Your face feels tight. You rack your brain to try to think of things they might ask. Your head is pounding. You go over your methods slide and check the language. You are restless. You can see it's 11am; you have to go now – the talk is only an hour away. It's hard to breathe. You think of Mitra's SRT talk – you don't want to end up like that. You feel choked up. You wonder what kind of feedback you'll get. Your whole body is tense. You head out and stop by the Neuroscience office to get the clicker and then walk to BCMM 206-208. You see the podium at the front of the room, but it looks different today. Your heart is pounding in your chest. You try to picture yourself behind it. Your breathing is shallow. You set up your computer and then sit down in the front row. There's a tight constriction in your chest. You check your watch: 11:57. You are so tense, you can't focus. You check your phone to make sure it's on silent, it shows 11:58. You are so jittery, you don't know how you can do this. Your stomach is in a knot. You just want to get away from here and all these awful feelings.

Participant 2: Low Intrinsic Spirituality (ISS = 1.2)

Stress Script 1

It's after 7pm on a dark and cold Thursday at the end of October. You are in your car driving in Westville, coming from yoga. You are trying to make a left turn off Whaley. You tense the muscles in your face and forehead. You are listening to the Arctic Monkeys. Your heart is beating quickly. As you try to make the turn, you suddenly feel yourself being thrown forward. Your head is rushing towards the steering wheel. Just as quickly, you feel yourself being flung back into your seat. Hard. Your whole body is tense. The car is spinning and you have no control over it. You feel the tight pull of the seatbelt cutting into your chest. There is a strange achy pain in your forehead. "Did I get a concussion?", you think "Did I hit hard enough?" You have an immediate headache. You feel nauseous. You get out of the car quickly and see the entire left side of the car is wrecked. A wave of panic comes over you. "Fuck!", you think "I'm in a car wreck!" You are jittery all over. You immediately think about what's going to happen with your insurance – you still have the Pennsylvania state plate. Your whole body is shaking. You can't believe this has happened. It's so cold outside – you can't stop your body from shaking. You're not sure what's going to happen. Your stomach is in a knot. You think about how you forgot to put the new insurance card in your wallet. How did all this happen? You didn't see the other car coming –they may have been speeding. You are so cold and so tense, you almost feel numb. You can't stop shaking. There is a sick feeling in your stomach. You just want to get away, away from here and all of these awful feelings.

Stress Script 2

It's after 3pm on a sunny weekday in November. You are in the lab at your computer. You quickly check to see if the reimbursement from the Boston trip has gone through. Your heart stops. Your bank account is in the negative. You gaze at the screen and see multiple bank fees added up. A heavy cold feeling comes over you. You need to call PNC bank and see if they can get the fees taken off. Your heart is beating quickly. You go into the computer room to use the landline. You grit your teeth. You close the door. You don't want your labmates to hear. You call PNC. You are so worked up you can't sit down. You try to explain to the guy on the phone your situation. You tighten the muscles in your face and forehead. "Oh, you're in the overdrawal protection program," he says. Your whole body is tense. You try to explain how they took money from your savings, but then kept adding fees to it. Your heart is beating faster now. "I'm going to talk to my manager," he says. You clench your jaw. He comes back and says: "We'll take off the one fee, but we can't get rid of the others." A wave of anger comes over you. You try to explain that fees were coming out both from the bank and from the company that bills were coming out of. You want to scream, or smash something. "I'm very sorry... but we can't help you anymore." he says. You hang up the phone. There is a sinking feeling in your chest. You think about how your plans and your savings got wrecked by something as stupid as bank fees. There is a lump in your throat. You think about how the refund won't even cover all the fees now. You feel stuck, like there's nothing you can do to change things. Between this and the car accident, all your savings are not only gone, but you owe them money. You try so hard, and nothing seems to ever work out. There is a deep intense pain sensation inside of you.

Participant 3: High Intrinsic Spirituality (ISS = 8.3)

Stress Script 1

It's 1am on a chilly Saturday night in October. You're wearing a pirate hat and glittery dress. You're at Toad's with Colin, Chandler and Darby. You heart is beating faster. The 4 of you are dancing. The club is really crowded – too crowded. You feel sweaty. People keep bumping into you as you dance. You tense the muscles in your body. Suddenly, you have a bad feeling about this. You reach down into your bag and realize that your phone is gone. Your heart stops. All your credit cards, your Yale ID, everything's in the phone case. A wave of panic comes over you: "Guys! My phone is gone! My phone is gone!" you yell. You're hot all over. They keep dancing as if nothing's wrong. "Don't worry, you'll find it!" you hear them say. It's hard to breathe. "Maybe I dropped it," you think. Your whole body is shaking. You get down on the ground and start crawling around. Your hands brush over the dirty floor, sticky with alcohol. Katy Perry's 'Dark Horse' is blaring through the club. Your head is pounding. You think about how your parents gave you the phone as a farewell gift just before you moved to the US. There's a lump in your throat. You can't believe you lost it so quickly. There is a feeling of panic inside you. You feel people stepping on your hands. Sweat is oozing out of you. From the floor, you can only see people's legs, and you realize you'll never be able to find your friends now. You want to smash something. You think about your credit card, your passport number for the visa, your phone contacts, all your photos: gone. There's a heavy feeling in your chest. Your friends don't care – nobody's sticking by you when you need them. You feel hot all over. You can't even contact anyone now. You feel stuck and alone. Everything's gone. These guys are clearly not your friends. Nobody's going to help you. Tears fill your eyes.

Stress Script 2

It's 9 pm on a cold weekday evening in March. You're in your room sitting at your desk checking emails on your laptop. Your heartbeat quickens. You see an email from Professor Lawrence. You tense the muscles in your face and forehead. You click on it and read: "We have noticed that you've violated a section of academic policy, we have forwarded this report and your paper to the executive committee. You will hear from them…" Your heart stops. "Oh my God – what have I done?", you think. Your face is flushed and you're trembling. You open the attached document and read: "…she took paragraphs with no references and presented them as her own…" Your heart is pounding in your chest. You remember how Professor Lawrence had said in class to check all your references. You're hot all over. You go online and quickly search the Executive Committee. It's hard to breathe. The website publishes reports on statistics and consequences for plagiarism: you read on and see half of the people get suspended or expelled. Your stomach is in a knot. Will this go on my disciplinary record? What will they do to me – the thoughts are racing through your head. You're choked up with a heavy feeling in your chest. You feel wave of panic all over your body. How will this affect my future, you think. You're tense all over. People are going to think of you as a cheater. You're gasping for air. You wrack your brain for a faculty member who could defend you in the hearing. A wave of shame comes over you. You think about what will happen when your friends find out. You feel hot all over. Everyone's going to think of you differently. Your heart is pounding in your chest. You can't believe this is happening. You know that any disciplinary action will take away your scholarship. You're restless and jittery. This could have all been avoided so easily. There's a sinking feeling in your chest. This will always hang over you. You just want to get away from here and all of these awful feelings. Tears fill your eyes.

Participant 4: High Intrinsic Spirituality (ISS = 8.7)

Stress Script 1

It's 6pm on a chilly, partly cloudy Sunday in October. You are at home in the computer room working on your English 101 Memory paper. Your stomach is in a knot. The paper is due tomorrow. Your heart is beating quickly. You are sitting on the desk chair in front of the laptop. You feel restless. The hours are going by and you keep rewriting the same section. Your palms are clammy as you try to type. "How can this be happening?" you think. There's a heavy feeling in your stomach. You had already started a rough draft, but none of the ideas are coming out. You feel beads of perspiration on your forehead. You stare at the Googledocs page open on the laptop. It's hard to breathe. Nothing is coming out right. You feel tense all over your back arms and legs. You reread Elizabeth Loftus' paper on false memories. Your heart is beating faster now. You start jotting down info. You want to scream or strike someone. None of the ideas are coming out right. You have cramps in your stomach. How are you ever going to get this done? There's a tight constriction in your chest. You keep going over the same section. You feel a lump in your throat. Finally, you look back at the Loftus paper. Your heart is pounding. A wave of panic comes over you. You've paraphrased the entire thing! You feel hot all over. "I'm dead" you think. You're gasping for air. It's after midnight now and you still have to do the citations and corrections. Your eyes are watering. How did this happen? Your whole body is shaking now. You think about how you've failed everyone: your parents, the class and Professor Robinson. You feel empty, drained and hollow inside. You've dug your own hole and now you're going to be buried in it. You feel stuck, like there's nothing you can do. There's a deep intense pain inside of you. It hurts to be alive.

Stress Script 2

It's 4pm on a rainy Sunday in September. You're at home in the computer room sitting in front of the laptop. You grit your teeth. You're working on Professor Jacoby's website for the equations. Your heart is beating faster. There are a lot of multiplication and division questions. You tense your back and arms. You finish the equation and hit enter on the keyboard. Your heart beats faster. A small box appears. Your stomach is in a knot. The box gives an explanation and hint to solve the equation. You feel sweaty. You try the equation again a second time. You are tense all over. Another box appears on the screen: "Wrong". You want to smash something. You can't believe you keep getting them wrong! Your whole body is shaking. The questions don't seem that hard, but you can't get any right! Your heart is pounding in your chest. You try a few more equations. You're hot all over. Even after the hint is provided, you still can't get them. You feel like crying. You see the 'wrong' box appear on the screen again and again. There's a sinking feeling in your chest. You've had problems with almost each of the 24 questions. You want to scream. You're stuck – there's nothing else you can do. Tears come to your eyes.

Professor Jacoby can see all the equations you got wrong too. It's hard to breathe. Everyone else in the class has probably already finished the equations with no problems. You're gasping for air. Why are you the only one who can't get it? You feel so helpless and alone. You think: "If I can't do this now, how am I going to survive exams?" There's a deep intense pain inside of you. It hurts

to be alive.