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# The neuroscience of spirituality, religion, and mental health: A systematic review and synthesis

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ABSTRACT

Prior research highlights the importance of spirituality/religion (S/R) as it relates to several aspects of mental health and clinical interventions. This research has been expanded to include the concurrent examination of neurobiological correlates of S/R to elucidate potential biological mechanisms. However, the majority of neurobiological research on S/R has neglected mental health, and the relationship across all three of these domains (S/R, mental health, and neurobiology) remains unclear. This study systematically reviewed research concurrently examining S/R, mental health, and neurobiology, and rated the methodological quality of included studies. Eighteen identified studies were then included in an integrated literature review and discussion, regarding the neurobiological correlates of S/R as it pertains to depression, anxiety, alcohol/substance misuse, and psychosis. The majority of studies demonstrated moderate to high methodological quality. Findings highlight the need for additional studies in this area as well as research that includes validated assessment of S/R.

## 1. Introduction

There has been a proliferation of mental health research examining spirituality/religion (S/R) in the last two decades (Zimmer et al., 2016). More recently, the field has examined S/R via neuroscientific methods (Phillips et al., 2020), including functional and structural neuroimaging, brain stimulation, and network mapping (van Elk and Aleman, 2017). For the purposes of this article, spirituality is broadly defined as one's subjective experiences of a "Higher Power"[1] and/or sense of connection with the transcendent as well as individuals' search for the sacred (Yaden and Newberg, 2016). Religion, on the other hand, is broadly defined as systems of beliefs and/or practices about a Higher Power and/or another transcendental force (Yaden and Newberg, 2016).

Prior research highlights the functional role of S/R as it relates to many aspects of mental health, including depression, suicide, alcohol/substance use, and functional impairment among people with severe mental illness (e.g., psychosis) (Garssen et al., 2021; Oxhandler et al., 2018; Beraldo et al., 2019; Schwalm et al., 2022; Anderson et al., 2015). It is also clear that S/R may be beneficial in mental health treatment as evidenced by research examining interventions for substance use (Beraldo et al., 2019), depression (Anderson et al., 2015), and anxiety (Anderson et al., 2015). The importance of S/R in mental health and mental health treatment has led to guidelines for psychiatrists regarding the incorporation of S/R in psychiatric practice (Charles et al., 2021). Research on mental health and psychiatry is broadly supported by neuroscience research indicating that S/R is related to certain brain regions and functioning. For example, growing evidence indicates that S/R is associated with protective mental health-related neurobiological correlates, including cortical thickness (Miller et al., 2014), decreased default mode network (DMN) connectivity (Svob et al., 2016), and greater posterior alpha (Tenke et al., 2013). These neurobiological correlates have been repeatedly associated with reduced risk of depression among adults and thus suggest a protective effect of S/R for mental health (Rim et al., 2019).

However, relatively little research to date has examined S/R, mental health, *and* their neurobiological correlates (Rim et al., 2019). The lack

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[1] For the purposes of the current article, Higher Power is characterized as a person's identification and/or characterization of the Divine, God, or Creator (Yaden and Newberg, 2016).

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of research in this area may be due to psychiatry's and clinical psychology's historical ignoring of S/R as it relates to mental health as well as the high costs of conducting research that examines neurobiological correlates (Rim et al., 2019). To compound the problem regarding the dearth of research on the neuroscience of S/R, reviews of research examining S/R, mental health, and neurobiological correlates are also rare (Rim et al., 2019). Indeed, to the authors' knowledge only one article has reviewed these topics to date, and its focus pertained primarily to neurobiology of S/R, with or without reference to mental health. Consequently, it remains unclear how and why neurobiological correlates of S/R are relevant to mental health and mental health treatment (Rim et al., 2019). It is essential to link and draw connections across these areas of research (i.e., S/R, mental health, and neurobiological correlates) in order to advance the understanding of how S/R may relate to neurobiological functioning and mental health via a sophisticated examination of potential causal mechanisms. Neurobiological research can, uniquely, allow researchers to investigate neural mediators and moderators of relationships between S/R and mental health. This research could support preventative and intervention efforts to improve mental health and treatment outcomes, for example, among individuals who identify as either religious/spiritual or non-religious/spiritual.

The present systematic review of the literature examines the extant research concurrently examining S/R, mental health, and neurobiological correlates. We assessed the characteristics of included studies (e.g., assessment of S/R, assessment of neurobiological correlate(s), and participant demographics) as well as the methodological quality of included studies. Overall, the goal of the current review was to synthesize research across levels of methodological quality identifying relationships across S/R, mental health, and neurobiological correlates as well as limitations and future directions for research in this area.

## 2. Methods

### 2.1. Eligibility criteria

Included studies were limited to peer-reviewed empirical research articles available in English, or articles in a different language for which English translations could be obtained. All articles measured spirituality, mental health (e.g., psychopathology), or a clinical population, and utilized neuroimaging (e.g., MRI, fMRI, DTI, PET). Due to the low number of overall studies, we also included papers that used electrophysiology (e.g., EEG). As such, all included articles included neuroimaging or EEG. Studies were excluded if they primarily assessed a neurological disorder that is not directly related to mental health (e.g., traumatic brain injury), did not use neuroimaging or EEG, or did not assess component(s) of spirituality or religiosity. In order to focus the scope of the current study, research that included assessment of secular mindfulness, or mindfulness to the exclusion of other aspects of spiritual life, was also excluded. For reviews of the neuroscience of mindfulness see Sezer et al. (2022) and Tang et al. (2015)

### 2.2. Search strategy

This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. A systematic search was conducted in the PubMed, EMBASE, PsycINFO via EBSCO, CINAHL via EBSCO, and Web of Science electronic databases. The search was performed on the 16th and 17th of February 2021. Our search criteria included terms such as "Neurobiology", "Neuroimaging", "Spirituality", "Religion", "Mental Health" and other related synonyms. An exhaustive list of terms searched can be found in Appendix A. We did not filter for language or time period in order to reduce selection bias. An initial screen was then performed to remove duplicate publications indexed by multiple databases.

### 2.3. Screening

Identified publications were screened in three phases. Phase one included an initial review of titles and abstracts from all articles by several study authors (MD, SM, PM, see Fig. 1). Articles that did not include both spirituality and mental health, and those that did not include neuroimaging or EEG were excluded. Articles written in a foreign language that did not have an English translation were also excluded. Phase two of publication screening included reading the text from articles that remained after phase one. This phase was also conducted by the above three authors. Two of these individuals reviewed each article and independently determined whether the article could be included in the review based on the eligibility criteria outlined above. In cases where concordance was not reached, the third reviewer assessed the paper as well. The third phase of publication screening included manual scanning of reference sections of relevant articles to identify additional papers that were not found during the initial electronic database search, and such articles were screened and reviewed using a similar process. Following these procedures, 18 papers were included in the final review (see Table 1).

### 2.4. Participant characteristics

The number of participants in the identified 18 studies ranged from 14 to 127 and the mean age of participants ranged from 16 to 70 years old. Of the studies, 83.3% included clinical samples and 16.7% included general community samples. Three studies included participants who were receiving psychiatric medication and six studies reported excluding participants taking psychiatric medication. Of note, the remaining studies did not report psychiatric medication intake or psychiatric medication prescription as exclusion criteria. Regarding spiritual and religious tradition, seven studies included majority Catholic samples, one study included a majority nondenominational Christian sample, and the remaining studies did not report on specific religious affiliations of the study participants.

### 2.5. Measurement of spirituality and mental health

Regarding the measurement of spirituality, five studies assessed religious services attendance, eight assessed S/R importance, three assessed self-transcendence using a self-report measure (i.e., Temperament and Character Inventory-Revised (Gutiérrez-Zotes et al., 2004), two assessed the experimental influence of prayer, one assessed intrinsic religiosity (i.e., general spirituality, religious devotedness, and commitment to religious lifestyle) (Pelletier-Baldelli et al., 2014), one assessed S/R well-being (i.e., meaning and purpose through connection with others and/or Higher Power (Unterrainer et al., 2017), one assessed spirituality as a component of psychological resilience, and one assessed the impact of spirituality on one's sense of self and relation to the world (see Table 2). There was heterogeneity in the rigor of spirituality measurement. That is, of the studies included in the review, three studies included validated measures of spirituality, two created and used specific item(s) assessing spirituality, thirteen used individual items from other measures, and two assessed engagement in religious tasks (e.g., prayer). See Tables 1 and 2 for more detail of S/R measurement.

Regarding the measurement of mental health across the 18 included studies, twelve assessed and reported results associated with measures of depression (e.g., Hamilton Depression Rating Scale [HAM-D] (Hamilton, 1960) and Beck Depression Inventory-II (Beck et al., 1996)), three assessed substance use, and two assessed psychosis or psychotic symptoms (for additional details see Tables 1 and 2). Of the three studies that examined anxiety as an aspect of mental health, only two reported results associated with measures of anxiety. Regarding assessment method, nine studies used diagnostic interviews to assess psychiatric diagnoses (e.g., Diagnostic Interview Schedule for Children (Lucas et al., 2001)), seven studies used validated self-report measures to assess

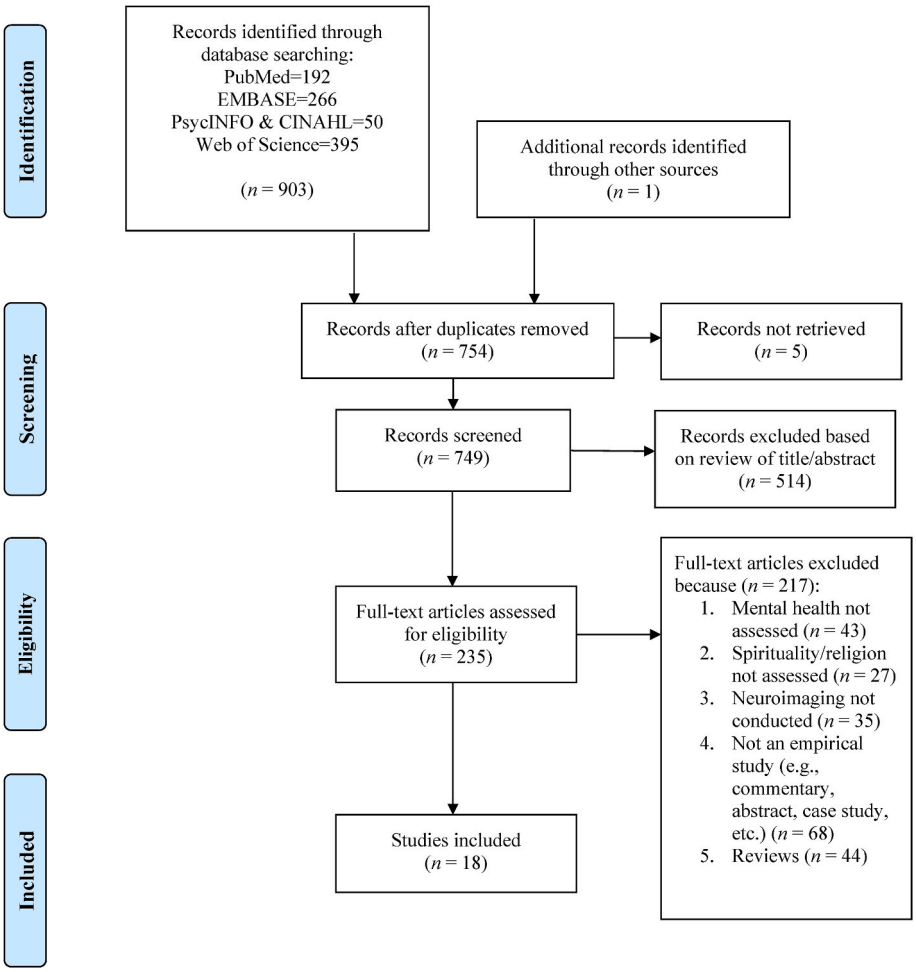


**Fig. 1.** Systematic review search results.

symptom severity, and two studies assessed mental health using author-created self-report measures not previously validated in the literature. Two studies assessed mental health (i.e., depression risk status) via the presence of a first-degree family member with a reported MDD diagnosis.

### 2.6. Methodological quality assessment

Two study authors (MD and PM) evaluated the methodological quality of included articles. Following the recommendation of Sanderson et al. (2007) (Sanderson et al., 2007), studies were categorized into "low quality," "moderate quality," or "high quality" based on three criteria: (1) post-hoc statistical power, (2) use of valid and reliable measures (of spirituality and/or mental health), and (3) clinical relevance of the study findings (e.g., clear ties between spirituality, mental health, and brain structure/functioning). Based on these criteria, studies were marked as "low quality" if they met none or one of these criteria, "moderate quality" if they met two of these criteria, and "high quality" if all three criteria were met. Consensus was reached by both raters regarding all but one article, which was subsequently evaluated by a third author (CCK) so a decision could be reached. Based on this scoring, we found that only three studies from all the included articles were of low quality (Makarec and Persinger, 1985; Simmons et al., 2012; Vlasova et al., 2018), and the rest of the articles were of moderate to high quality (Miller et al., 2014; Svob et al., 2016; Tenke et al., 2013, 2017; Pelletier-Baldelli et al., 2014; Unterrainer et al., 2017; Galanter et al., 2017; Baldwin et al., 2016; Bouso et al., 2015; Karlsson et al., 2011; Kayser et al., 2019; Li et al., 2019; Miller and Barton, 2015; Panier et al., 2020; Liu et al., 2017).

### 2.7. Brain imaging and electrophysiology

Of the included studies, six used structural Magnetic Resonance Imaging (MRI), five Electroencephalography (EEG), four Diffusion Tensor Imaging (DTI), two Functional Magnetic Resonance Imaging, and one Positron Emission Tomography (PET).

## 3. Results

For ease of interpretation, in the following sections we categorized studies according to the aspect of mental health or psychopathology assessed (e.g., depression, alcohol/substance use).

### 3.1. Depression

Our literature review identified a total of thirteen studies (Miller et al., 2014; Svob et al., 2016; Tenke et al., 2013, 2017; Simmons et al., 2012; Vlasova et al., 2018; Baldwin et al., 2016; Karlsson et al., 2011; Kayser et al., 2019; Li et al., 2019; Miller and Barton, 2015; Panier et al., 2020; Liu et al., 2017) that examined relations among spirituality/religiosity, depression, and neurobiology. However, as noted below, several of these studies emerged from the same database, so caution is urged in interpretation. We have divided these studies below into two topical sections: *Familial Risk for Depression* and *Current Depressive Symptomatology*.

*Familial Risk for Depression.* Of the twelve studies identified that

**Table 1**
*Summary of Included Papers.*

| Author & Year | Mental Health | S/R | Imaging Method | Purpose | Main Findings |
|---|---|---|---|---|---|
| Baldwin et al., 2016 | Depression (HAM-D) and Anxiety (HAM-A) | Daily Spiritual Experiences Scale; Life Orientation Test; 6-week prayer intervention | Functional Magnetic Resonance Imaging (fMRI) | To assess clinical and neural changes related to prayer intervention. | Participants experienced a reduction in depression and anxiety after the 6-week prayer intervention and at 12-month follow-up.<br>Subjects demonstrated increased activation in the prefrontal cortex during traumatic stimulus exposure compared to pre-treatment scans. Participants who experienced the greatest reduction in depressive symptoms displayed increased activation in the left inferior frontal gyrus.<br>Prayer intervention may alter brain activity such that it reduces activation in brain regions responsible for negative emotions. |
| Bouso et al., 2015 | Symptoms of psychopathology and personality | Self-Transcendence | Magnetic Resonance Imaging (MRI) | Examine differences between Ayahuasca users and controls in cortical thickness (CT), and personality factors (including spirituality). | Self-transcendence and subscales of self-transcendence (e.g., spiritual acceptance, self-forgiveness, and transpersonal identification) were greater among ayahuasca users, whereas psychopathology was equivalent between the groups<br>Spirituality was correlated with CT in posterior cingulate cortex (PCC) among both ayahuasca users and controls. |
| Galanter et al., 2017 | Alcohol misuse | Prayer vs. control conditions | fMRI | Examine neural correlates of reduced alcohol craving after reading Alcoholics Anonymous (AA) prayers in individuals with long-term sobriety. | Participants who read prayers prior to viewing craving-inducing images reported less alcohol craving.<br>Increased activation was seen in brain areas related to self-referential processing and the default mode network in the prayer condition.<br>Prayer may be associated with activation in brain regions associated with alcohol cravings. |
| Karlsson et al., 2011 | Depression (HAM-D)<br>Temperament and Character | Self-transcendence | Positron Emission Tomography (PET) | Determine if ligand serotonin 1A receptor binding was inversely related to spirituality in clinically depressed or non-depressed subjects. | No significant correlations were observed between self-transcendence and serotonin 1A receptor binding in any of the brain regions studied in either clinically depressed or non-clinically depressed subjects.<br>Self-transcendence may not be associated with receptor availability associated with risk for depression. |
| Kayser et al., 2019 | Familial risk for depression<br>(high vs. low) | Single item assessing S/R importance | Electroencephalogram (EEG) | Examine whether abnormal premature event-related potential (ERP) activation in response to negative stimuli was moderated by importance of S/R for adolescent and adult patients at high or low familial risk for MDD. | High S/R was associated with lower ERP response for high risk participants but high S/R was associated with increased ERP response for low-risk participants.<br>Low S/R importance was associated with greater ERP responsivity to negative stimuli in the right hemisphere regardless of risk.<br>High S/R importance may be a source of resilience for individuals with high risk of familial depression and may be associated with affect regulation. |
| Li et al., 2019 | Familial risk for depression (high vs. low)<br>Symptoms of affective and psychotic disorders | Importance of Spirituality/ Religion (S/R)<br>Service attendance<br>Affiliation | Diffusion Tensor Imaging (DTI) | Extend prior research examining brain structure differences associated with Major Depressive Disorder (MDD) risk and examine differences across high-risk and | Participants with high religious importance and high familial risk for MDD did not have significant white matter differences in brain areas implicated in depression, including the frontal lobes, |

(*continued on next page*)

**Table 1** (*continued*)

| Author & Year | Mental Health | S/R | Imaging Method | Purpose | Main Findings |
|---|---|---|---|---|---|
| | | | | low-risk individuals who report S/R importance. | precuneus, and temporal lobes. Results suggest religious importance reduces brain structure differences typically associated with familial risk for depression. |
| Liu et al., 2017 | Familial risk for MDD (high vs. low) | Single item assessing S/R importance | MRI | Identify potential neural substrates underlying the relationship between S/R and familial depression risk and build upon previous data investigating cortical volume. | High importance of S/R was associated with thicker cortex and larger pial surface area in multiple brain regions in individuals at high risk for MDD. |
| | | Frequency of service attendance | | | Religious service attendance was not associated with cortical regions. Religiosity may be associated with a biological marker of resilience among individuals at high risk for MDD. |
| Makarec and Persinger, 1985 | Mental health and personality | Personal Philosophy Inventory | EEG | Measurement, validation, and examination of the relationship between religious beliefs, mystical experiences and EEG activity in the temporal lobe. | Degree of temporal lobe activity was positively correlated with self-reported rates of mystical experiences and religious beliefs. Individuals who reported religious experiences also showed higher temporal lobe and subcluster activity than those who did not report religious experiences. |
| | | Religious affiliation | | | No significant differences across religious affiliation were observed. |
| Miller and Barton, 2015 | Symptoms of psychopathology | Self-transcendence subscale of the Temperament and Character Inventory | MRI | Examine whether self-transcendence (low vs. high) moderates neural and brain structure correlates of depression among adolescents. | Among individuals high in self-transcendence, depressive symptoms were associated with higher CSF and extracerebral CSF volume. Among individuals low in self-transcendence, depressive symptoms were negatively correlated with right cerebellum volume. Self-transcendence (low vs. high) significantly interacted with the relationship between depressive symptoms and left occipital gray matter. Spirituality may be associated with brain structures responsible for adaptation and emotional attunement in adolescents. |
| Miller et al., 2014 | Familial risk for depression (high vs. low) | Importance of S/R | MRI | Examine association between S/R and CT in adults with high and low depression risk. | Importance of S/R was associated with greater cortical thickness (CT) in parietal and occipital regions, medial frontal lobe of the right hemisphere, and the cuneus and precuneus in the left hemisphere, independent of familial risk. |
| | | Service attendance | | | Frequency of service attendance was not significantly associated with neural correlates. |
| | | Affiliation | | | The effects of S/R importance on CT in the medial wall of the left hemisphere were stronger in high-risk individuals |
| Panier et al., 2020 | Depression and Anxiety | Single-item assessing importance of S/R | EEG | Examine the role of posterior EEG alpha and S/R on predicting symptoms of depression in families with high depression risk in a longitudinal study. | Greater S/R importance was associated with less depression severity over time. Lower depression severity was associated to greater S/R importance at low alpha levels. At high alpha levels, lower depression severity was associated with lower R/S importance. |
| Pelletier-Baldelli et al., 2014 | Symptoms of Non-Clinical Psychosis | Duke University Religion Index | MRI | Examine religiosity in individuals with NCP and | Individuals with NCP reported higher levels of intrinsic religiosity. |

(*continued on next page*)

**Table 1** (*continued*)

| Author & Year | Mental Health | S/R | Imaging Method | Purpose | Main Findings |
|---|---|---|---|---|---|
| | | | | investigate associations with brain structures. | Religiosity was not significantly associated with neural correlates sample-w. A statistical trend was found between intrinsic religiosity and reduced left medial orbitofrontal cortex (OFC), right medial OFC, and right lateral OFC. |
| Simmons et al., 2012 | Depression and Anxiety<br>Personality<br>Impact of self on world, and world on self | Combined impact of spirituality on self and world | DTI | Create a measure to quantify the individual's adaptation to adulthood from adolescence among individuals with and without a history of drug abuse. | Impact of spirituality negatively correlated with white matter integrity in the right anterior thalamic radiation, and with gray matter density of the following brain structures: right cingulate gyrus, left superior temporal gyrus, and right cerebellum. Results suggest spirituality is associated with reduced density across several brain structures in young adults with and without drug abuse history. |
| Svob et al., 2016 | Familial risk for major depressive disorder (MDD)<br><br>(high vs. low) Symptoms of affective and psychotic disorders | Importance of S/R as assessed by item on the Schedule for Affective Disorders and Schizophrenia-Lifetime | Resting-state functional connectivity MRI | Examine whether S/R importance moderates default mode (DMN) network connectivity in individuals with a familial risk of depression. | High R/S importance was associated with decreased DMN connectivity among individuals with high risk for MDD but not for those with low risk.<br>S/R importance was not significantly associated with the central executive network circuity. |
| Tenke et al., 2013 | Familial risk of depression (high vs. low) | Single-item assessing S/R importance | EEG | To examine whether individuals who differed in strength of S/R beliefs also differed in EEG alpha in a longitudinal study. | Participants who rated S/R as highly important at initial assessment showed greater alpha compared to those who did not. Those who rated S/R as important in both sessions showed greater alpha than those who changed their ratings over a ten-year period. |
| Tenke et al., 2017 | Familial risk for depression (high vs. low) | Single-item assessing S/R importance<br><br>Religious service attendance<br><br>Religious Affiliation | EEG | Extend and replicate prior research examining the relationship between importance of S/R and posterior EEG alpha with new data from a 20-year follow-up. | Participants who initially rated S/R as highly important displayed greater alpha compared to those who did not, even if their S/R rating later increased over a 20-year period.<br>Changes in religious denomination were associated with decreased alpha over a 20-year period.<br>S/R importance may be protective against neural correlates of depression and changing religious affiliation may be a risk factor for neural correlates of depression over time. |
| Unterrainer et al., 2017 | Poly-drug use disorder (PUD) | Multidimensional Inventory for Religious/Spiritual Well-Being | DTI | Examine whether there is a connection between white matter (WM) integrity and attachment styles, as well as various affective states, including spirituality, in individuals with PUD. | No notable correlations were observed between spirituality and white matter integrity in individuals with PUD, recreational substance users, or non-using controls. |
| Vlasova et al., 2018 | Resilience in older adults with Major Depression | Spirituality (as a component of resilience—Connor-Davidson Resilience Scale) | DTI | Identify neural correlates of four components of resilience in geriatric individuals with depression. | No significant neural correlates with spirituality were found. |

examined depression, eight examined familial risk for depression (Miller et al., 2014; Svob et al., 2016; Tenke et al., 2013, 2017; Kayser et al., 2019; Li et al., 2019; Panier et al., 2020; Liu et al., 2017). All eight of these studies included data solely from the same, largescale, multi-generational, longitudinal study, that examined families with high and low familial risk for depression (Weissman et al., 2005). Familial risk level was determined by the presence of a first-degree family member with an MDD diagnosis and current depression was determined via standardized clinical interview (Weissman et al., 2005) (the Schedule for Affective Disorders and Schizophrenia—Lifetime Version) (Mannuzza et al., 1986) Across all eight studies, spirituality/religion importance was assessed by three widely used items to assess S/R (Phillips et al., 2020).

Regarding the assessment of neurobiological correlates, three of these studies used MRI to assess cortical thickness (Miller et al., 2014; Svob et al., 2016; Liu et al., 2017). Two of these studies indicated that

**Table 2**
*Methodological Quality* of *Included Studies.*

| Author & Year | Sample | Study Design | Statistical Power (post-hoc) | Valid and Reliable Measures (±) | Importance of Findings (±) | Methodological Quality Rating |
|---|---|---|---|---|---|---|
| Baldwin et al., 2016 | 14 clinically depressed adults | Within subjects<br>Experiment/ Treatment Study | (+) 0.93 | (+) Spirituality/Religion (S/R) measured by the Daily Spiritual Experiences Scale, a validated self-report spirituality measure.<br>Includes well established observer rated clinical measures (Hamilton Rating Scales for Depression and Anxiety (HAM-A, HAM-D)). | (+) Substantial. Participants experienced decreases in depression and anxiety, as well as different brain activation patterns after a prayer intervention. | 3<br>High |
| Bouso et al., 2015 | 44 adults (22 Ayahuasca users, 22 controls) | Between subjects<br>Cross-sectional | (+) 0.97 | (+) S/R measured by the self-transcendence dimension of the Temperament and Character Inventory – Revised (TCI-R), a validated personality scale.<br>Clinical psychopathology measured by a validated self-report measure (Symptom Checlist-90-Revised). | (−) Minimal. No significant difference in psychopathology between users and non-users. No significant associations between psychopathology and S/R measures or neuroimaging. | 2<br>Moderate |
| Galanter et al., 2017 | 20 Alcoholics Anonymous (AA) members with long-term abstinence | Within subjects<br>Cross-sectional | (+) 0.99 | (+) S/R affiliation measured by items used in US national surveys.<br>Measures of alcohol use and craving included items used in previous studies. | (+) Substantial. Demonstrates that there is a neural basis for AA prayers' effect on craving reduction. This suggests that AA prayers could be used to help reduce craving for alcohol. | 3<br>High |
| Karlsson et al., 2011 | 43 adults (23 clinically depressed adults, 20 healthy controls) | Between subjects<br>Cross-sectional | (+) 0.99 | (+) S/R measured by the self-transcendence dimension of the TCI-R, a validated personality scale.<br>Includes validated self- report measures on personality and clinical symptoms (TCI, HAM-D, Beck Depression Inventory (BDI)). | (−) Minimal. Findings do not support the author's theory that the serotonin system underlies spirituality in a clinical population. | 2<br>Moderate |
| Kayser et al., 2019 | 127 individuals (74 high-risk, 53 low-risk) | Between subjects<br>Cross-sectional | (+) 0.97 | (+) S/R measure has been shown to correlate with the Fetzer Institute Full-scale measure of personal spirituality.<br>Includes validated clinical interview and self-report measures (Schedule for Affective Disorders and Schizophrenia-Lifetime Version (SADS-L), HAM-D). | (+) Substantial. Findings indicate that there is a neurological basis for protective high S/R beliefs in participants at familial risk for Major Depressive Disorder (MDD). | 3<br>High |
| Li et al., 2019 | 99 adults (53 high-risk, 46 low-risk) | Between subjects<br>Cross-sectional | (+) 0.99 | (+) S/R measured by items used widely in literature on spirituality and health.<br>Included a validated diagnostic interview measure (SADS-L). | (+) Substantial. Findings indicate that high importance of S/R could be protective of deleterious impacts on brain microstructure associated with familial risk of depression. | 3<br>High |
| Makarec and Persinger, 1985 | 28 students (10 poets, 18 controls) | Between subjects<br>Cross-sectional | (−) 0.25 | (+) Validated the Personal Philosophy Inventory which included clusters of items assessing religious beliefs.<br>Included a validated clinical diagnostic scale (Minnesota Multiphasic Personality Inventory). | (−) Minimal. Temporal lobe spikes correlated with S/R variables. Authors indicate these variables may be associated with schizotypal personality disorder. No significant associations between other S/R measures and either electroencephalogram (EEG) or mental health measures. | 1<br>Low |
| Miller and Barton, 2015 | 125 healthy adolescents (54 high, 71 low self-transcendence) | Between subjects<br>Cross-sectional | (+) 0.85 | (+) S/R measured by the self-transcendence dimension of the TCI-R, a validated personality scale.<br>Included a validated diagnostic measure (Diagnostic Interview Schedule for Children Predictive Scales) | (+) Substantial. Provides support of distinct clinical and neural correlates for a sub-type of depression related to emergence of transcendence.<br>Suggests that treatments addressing these differences may be most effective for adolescents with high transcendence suffering with depressive symptoms. | 3<br>High |
| Miller et al., 2014 | 103 adults (67 high-risk, 36 low-risk) | Between subjects | (+) 0.85 | (+) S/R assessed by items widely used in research on spirituality and health. | (+) Substantial. Suggests a neural basis (increased cortical thickness in parietal and occipital areas) for a | 3 |

(*continued on next page*)

**Table 2** (*continued*)

| Author & Year | Sample | Study Design | Statistical Power (post-hoc) | Valid and Reliable Measures (±) | Importance of Findings (±) | Methodological Quality Rating |
|---|---|---|---|---|---|---|
| | | Longitudinal | | Included validated clinical self-report measures (HAM-D, HAM-A) | protective role of religious importance in people with a family history of depression. | High |
| Panier et al., 2020 | 94 adults (59 high-risk and 35 low-risk) | Within subjects<br>Longitudinal | (−) 0.73 | (+) S/R importance measured by a validated single survey item.<br>Included validated clinical self-report measures (Patient Health Questionnaire-9, Inventory of Depression and Anxiety Symptoms II) | (+) Moderate. Demonstrates a relationship between S/R importance and depression severity that is moderated by EEG alpha. | 2<br>Moderate |
| Pelletier-Baldelli et al., 2014 | 40 adolescents (20 with non-clinical psychosis (NCP), 20 healthy controls) | Between subjects<br>Cross-sectional | (−) 0.35 | (+) S/R measured by a validated self-report measure, the Duke University Religion Index.<br>Included validated clinical self-report and diagnostic measures (Community Assessment of Psychic Experiences, Structured Clinical Interview for DSM-IV Disorders) | (+) Moderate. Demonstrated certain brain abnormalities may be linked to NCP and elevated intrinsic religiosity. Suggests these brain differences associated with NCP may also confer a heightened susceptibility for religiosity | 2<br>Moderate |
| Simmons et al., 2012 | 65 young adults (36 with history of substance use, 29 healthy controls) | Between subjects<br>Cross-sectional | (−) 0.55 | (+) Tested and validated a new self-report measure Self and World Expressions Evaluation (SWEET) which included an S/R factor.<br>Included well established clinical (BDI-II, STAI), personality (NEO-Five Factor Inventory, and neuropsychological measures (California Verbal Learning Test version II, Delis-Kaplan Executive Function System) | (−) Minimal. The spirituality factor of the SWEET correlated negatively with white matter integrity and gray matter density in several brain regions. No strong associations between S/R neural correlated and psychiatric measures were identified. | 1<br>Low |
| Svob et al., 2016 | 104 individuals<br>(57 high-risk, 47 low-risk) | Between subjects<br>Longitudinal | (+) 0.99 | (+) S/R importance measured by a validated single survey item.<br>Used previously validated clinical diagnostic and self-report measures (SADS-L, Parental Bonding Instrument) | (+) Substantial. S/R importance was indirectly correlated with low DMN connectivity, which may be protective in individuals at risk for familial depression. | 3<br>High |
| Svob et al., 2016 | 106 adults (57 high-risk, 49 low-risk) | Between subjects<br>Longitudinal | (+) 0.99 | (+)S/R importance measured by a validated single survey item.<br>Used previously validated clinical diagnostic and self-report measures (SADS, Kiddie-SADS)) | (+) Substantial. Demonstrated relationship between S/R importance and cortical thickness and surface area in high-risk group. Prior research has shown that individuals with high familial risk of depression have reduced cortical thickness. This implies that R/S importance serves as a protective factor in individuals at high familial risk for depression. | 3<br>High |
| Tenke et al., 2013 | 52 adults | Within subjects<br>Between subjects<br>Longitudinal | (+) 0.99 | (+) S/R importance measured by a validated single survey item.<br>Risk status for depression was determined by the presence of a first degree relative with a diagnosis of MDD. | (+) Substantial. Participants who rated R/S as highly important at initial assessment displayed greater EEG alpha compared to those who did not. Those who rated R/S important in both sessions showed greater alpha than those who changed their ratings. EEG alpha differences were particularly well-defined for participants with lifetime depression<br>Findings suggest there may be a critical stage for the development of spirituality. | 3<br>High |
| Tenke et al., 2017 | 73 adults | Within subjects<br>Between subjects<br>Longitudinal | (+) 1.00 | (+)S/R importance measured by a validated single survey item.<br>Risk status for depression was determined by the presence of a | (+) Substantial. Demonstrated that initial rating of S/R importance predicted greater resting state posterior EEG alpha (associated with better pharmacologic treatment outcomes for clinical depression), compared to those who had not | 3<br>High |

(*continued on next page*)

**Table 2** (*continued*)

| Author & Year | Sample | Study Design | Statistical Power (post-hoc) | Valid and Reliable Measures (±) | Importance of Findings (±) | Methodological Quality Rating |
|---|---|---|---|---|---|---|
| | | | | first degree relative with a diagnosis of MDD. | initially rated high S/R, even if their ratings increased later. Changing religious denomination was associated with lower alpha levels compared with keeping the same religious denomination. Findings suggest there may be critical stage in the development of S/R that is linked to posterior resting EEG alpha. | |
| Unterrainer et al., 2017 | 59 adults (19 with Poly-drug use disorder (PUD), 20 with recreational substance use, 20 non-using controls) | Between subjects<br>Cross-sectional | (+) 0.87 | (+) S/R well-being was assessed by the Multidimensional Inventory for Religious/ Spiritual Well-Being<br>Included validated self-report scales assessing personality (Adult Attachment Scale, Brief Affective Neuroscience Personality Scale (BANPS) | (−) Minimal. No significant findings relating to S/R and neuroimaging/ mental health other than a tendency ($p = 0.11$) for decreased spiritual well-being in PUD patients. Results did indicate a significant positive correlation between the "CARE" subscale of BANPS and spiritual well-being. | 2<br>Moderate |
| Vlasova et al., 2018 | 70 older adults with MDD | Cross-sectional | (−) 0.36 | (+) S/R assessed by spirituality component of the Connor-Davidson Resilience Scale (CD-RISC) | (−) Minimal. No significant associations between S/R and neuroimaging data. | 1<br>Low |

self-rated importance of spirituality/religion was associated with greater cortical thickness, specifically in the cuneus and precuneus regions of the bilateral parietal and occipital regions. This was particularly the case among individuals who were at high-risk of developing depression (i.e., children of depressed parents) (Miller et al., 2014; Svob et al., 2016). These results were interpreted as indicating that high importance spirituality/religion may protect against depression by either increasing cortical thickness or preventing cortical thinning. The third study, indicated that the importance of S/R was associated with thicker cortex and higher pial surfaces among individuals at high-risk for depression (Liu et al., 2017). Additionally, increased white matter was also observed in the superior and middle frontal gyrus, bilateral insula, supplementary motor area, and postcentral gyrus among individuals who reported high importance of S/R and had a high familial risk of depression (Liu et al., 2017). Given these findings, the investigators suggested that S/R importance may confer neurobiological benefits (Liu et al., 2017). As these studies were conducted with individuals with and without a history of parental depression, it was suggested that these effects may be particularly protective against developing depression for individuals who have depressed parents.

Li et al. (2019) (Li et al., 2019) examined the relationship between S/R and depression among individuals at low and high risk of depression using DTI to assess ellipsoidal area ratio (EAR), which is comparable to fractional anisotropy, among adults at high- and low-risk for depression, with either high or low self-rated importance of S/R. Higher EAR is indicative of greater microstructural integrity, which is believed to be indicative of stronger connections in the brain and healthier white matter (Li et al., 2019). Results indicated that participants with high familial risk of depression and high importance of R/S beliefs, demonstrated reduced EAR in white matter in the following areas: left superior, and middle frontal gyrus, left superior parietal lobule, and right supplementary motor area (Li et al., 2019). In addition, among participants with high familial risk of depression and low importance of R/S beliefs, individuals demonstrated significantly decreased EAR in the following white matter regions: precuneus, superior parietal lobe, superior and middle frontal gyrus, and bilateral insula, supplementary motor area, and postcentral gyrus (Li et al., 2019). Results led authors to hypothesize that R/S beliefs may confer resilience among individuals with high familial risk of depression.

One study examined neural connectivity and temporal activity patterns and relations between S/R and familial risk of depression. Svob and colleagues' (2016) (Svob et al., 2016) findings revealed that high S/R importance was associated with decreased default mode network (DMN) connectivity in the left parietal lobe but not the precuneus or within the Central Executive Network (CEN) among individuals at high-risk of depression. The investigators concluded that the importance of S/R may protect against depression by way of reducing baseline neural connectivity in the left lateral parietal lobe during resting state in children and adults.

Three studies (Tenke et al., 2013, 2017; Panier et al., 2020) used EEG to examine longitudinal relationships between self-reported importance of S/R, depression, and neural activity, among individuals with high and low risk of depression. Tenke and colleagues (2013, 2017) (Tenke et al., 2013, 2017) found that individuals who self-reported high importance of S/R were associated with greater alpha power in posterior EEG at baseline, as well as at 10-year and 25-year follow-up. Results from Panier et al. (2020) (Panier et al., 2020) corroborated these findings with similar results, suggesting that individuals reporting high importance of S/R at age 21 predicted fewer depressive symptoms at 25-year follow-up, among individuals at high risk of depression.

Kayser et al. (2019) (Kayser et al., 2019) examined relations among S/R and familial risk for depression, using event related potentials (ERPs), a measure of transient brain and neural activity, and in response to events or stimuli. Results indicated that early ERP responsivity to negative and neutral stimuli differed across individuals who report high versus low importance of S/R, and high- and low-risk for developing depression. Individuals reporting high importance of S/R who were also high-risk for developing depression were associated with slower ERP responsivity to negative stimuli. The authors interpreted this result to mean that the importance of S/R may be associated with lower reactivity and reduced risk for developing depression among high-risk individuals.

*Current Depressive Symptomatology*. Four studies examined relations among S/R, current depressive symptoms, and neurobiology (Simmons et al., 2012; Vlasova et al., 2018; Karlsson et al., 2011; Miller and Barton, 2015). Of these, two studies examined adolescent samples (Simmons et al., 2012; Miller and Barton, 2015), one examined an adult sample (Karlsson et al., 2011), and one examined a geriatric sample (Vlasova et al., 2018). Two studies used DTI (Simmons et al., 2012; Vlasova et al., 2018), one used MRI (Miller and Barton, 2015), and one used PET (Karlsson et al., 2011).

Simmons et al. (2012) (Simmons et al., 2012) assessed spirituality using a study-specific questionnaire that assessed the degree to which individuals are impacted by the spiritual world/spirituality and how they impact the spiritual world/spirituality. Using DT, authors found

that greater spirituality was associated with decreased white matter integrity in the right anterior thalamic radiation and reduced gray matter density in the right cingulate gyrus, left superior temporal gyrus, and the right cerebellum. In contrast, Vlasova et al. (2018) (Vlasova et al., 2018) examined spirituality as a component of psychological resilience, and their findings did not reveal significant relations between spirituality and neurobiology in a geriatric sample. Thus, across these studies, relations among S/R, depressive symptoms, and neurobiology remain unclear. It is notable that both of these studies (Simmons et al., 2012; Vlasova et al., 2018) met our criteria for low methodological quality. This was due to both studies reporting low statistical power and the lack of strong statistical associations to inform conclusions. Specifically, in this case and others low statistical power refers a statistical test having a relatively small chance of detecting a "true effect" and/or that the results are likely to be distorted by random and systematic error. Satistical power is influenced by sample size, effect size, and significance level (Cohen, 1992).

One study used MRI to examine relations among depression and spirituality among adolescents (Miller and Barton, 2015). In this study, spirituality was assessed as an aspect of self-transcendence, which was operationalized as the extent to which an individual feels connected with oneself, others, nature, and a Higher Power (Miller and Barton, 2015). Results indicated that among adolescents with high self-reported self-transcendence, high depressive symptoms were associated with higher volumes of cerebrospinal fluid (CSF) and extracerebral spinal fluid. However, among adolescents with low self-transcendence, depression was associated with reduced CSF volume. Additionally, adolescents with high self-transcendence were associated with reduced occipital gray matter, and lower sub-threshold depression scores as compared to the adolescents who reported low self-transcendence. The investigators suggested that these results indicate that adolescents with both high self-transcendence and high depressive symptoms may show signs of "alarm or need for adaptation," while self-transcendence may protect against depression in later adulthood overall (Miller and Barton, 2015). Authors reached this conclusion because high CSF and extracerebral spinal fluid may be indicative of adaptation (Miller and Barton, 2015).

Another study used PET to examine relations among serotonin 1A receptor binding (i.e., ligand binding) and self-transcendence across participants with and without clinical depression (Karlsson et al., 2011). Results did not reveal significant associations across self-transcendence and ligand binding in the following brain regions: amygdala, anterior cingulate cortex, dorsal raphe nuclei, dorsolateral prefrontal cortex, angular gyrus, inferior, middle, and superior temporal gyri, medial prefrontal cortex orbitofrontal cortex, hippocampus, insular cortex, subgenual anterior cingulate cortex, supramarginal gyrus, ventrolateral prefrontal cortex, and posterior cingulate cortex among either depressed or non-depressed participants. These results led the authors to argue that there is not sufficient evidence to conclude that neural serotonin systems are integral to spiritual experiences among individuals with and without clinical depression (Karlsson et al., 2011).

### 3.2. Alcohol/substance use

Three studies examined relations among S/R, alcohol/substance use, and neurobiology (Unterrainer et al., 2017; Galanter et al., 2017; Bouso et al., 2015). Two studies examined these relations using MRI. The results from these two studies are inconsistent. Specifically, Bouso et al. (2015) (Bouso et al., 2015) examined religiousness, spirituality, and self-transcendence in a cohort of psychedelic (Ayahuasca) users and non-psychedelic users. Among Ayahuasca users, as opposed to controls, lower cortical thickness was associated with higher self-transcendence, religiousness, and spirituality. Bouso et al. (2015) (Bouso et al., 2015) speculated that Ayahuasca use may alter brain structure that may in turn support increased S/R. Unterrainer et al. (2017) (Unterrainer et al., 2017) examined S/R well-being and white matter integrity among adult men who were recreational drug users or poly-drug use disorder. Results were not significant.

Another experimental study using fMRI, examined the relationship between engaging in prayer, alcohol cravings, and neural processes, among long-term abstainers from Alcoholics Anonymous (Galanter et al., 2017). Results indicated that individuals in the prayer condition experienced less alcohol-craving when exposed to an alcohol-related image, and also demonstrated increased activation in left-anterior middle frontal gyrus, left superior parietal lobule, bilateral precuneus, and bilateral posterior middle temporal gyrus. Furthermore, craving following prayer was inversely correlated with activation of these brain regions (Galanter et al., 2017). The authors suggest that findings support the theory that prayer may concurrently reduce alcohol cravings and increase neural processes associated with attention and control (Galanter et al., 2017).

### 3.3. Anxiety

Two studies examined relations among S/R, anxiety, and neurobiology (Simmons et al., 2012; Baldwin et al., 2016). Both of these studies reported statistically insignificant results. Baldwin et al. (2016) (Baldwin et al., 2016) assessed anxiety using the Hamilton Rating Scale for Anxiety (HAM-A) (Hamilton, 1959) and spirituality using the Daily Spiritual Experiences Scale (Underwood and Teresi, 2002) among 14 subjects in a six-week prayer intervention and fMRI-based task. Significant relations among anxiety, spirituality, and neurocorrelates were not found. Simmons et al. (2012) (Simmons et al., 2012) investigated the relationship across white matter integrity DTI data, anxiety, as measured by the State Trait Anxiety Inventory, (Spielberger et al., 1983) and spirituality via two author-created items (i.e., "What is your spiritual impact on the spiritual world?" and "What is the spiritual world's spiritual impact on you?"). Analyses did not result in significant findings (Simmons et al., 2012). Of note, Panier et al. (2020) (Panier et al., 2020) reported use of the Inventory of Depression and Anxiety (Watson et al., 2012) but did not report analyses examining anxiety in their study.

### 3.4. Psychosis

One study examined relations among S/R, psychosis, and neurobiology (Pelletier-Baldelli et al., 2014). This study conducted by Pelletier-Baldelli et al. (2014) (Pelletier-Baldelli et al., 2014) included adolescents with and without non-clinical psychosis (NCP). Within this study, NCP was characterized by sub-clinical psychotic-like symptoms that did not meet criteria for a formal psychotic disorder diagnosis (Pelletier-Baldelli et al., 2014). MRI was used to examine Orbitofrontal Cortex (OFC) volume, in addition to self-reported intrinsic religiosity as assessed by the Duke University Religion Index (Koenig and Büssing, 2010). Intrinsic religiosity is different from other forms of religiosity (i.e., extrinsic religiosity) in that it encompasses one's commitment to leading a religious lifestyle and following the tenets of an S/R tradition (Pelletier-Baldelli et al., 2014). Results included higher self-reported religiosity among individuals with NCP as compared to the control group. In addition, among individuals with NCP, higher religiosity was associated with reduced bilateral volume in the lateral and medial OFC. Across the entire sample, higher intrinsic religiosity was associated with decreased left medial, right medial, and right lateral OFC. Among individuals without NCP, higher religiosity was associated with greater positive symptoms of psychosis. The investigators concluded that structural brain differences associated with NCP are also associated with increased religiosity.

## 4. Discussion

The primary aim of the present study was to conduct a systematic literature review of published research that concurrently examined relations among S/R, mental health, and neurobiological correlates. A

secondary aim of this study was to examine the methodological quality of identified studies. After initial identification of 903 studies, a final total of just 18 studies were included in this review after systematic filtering and screening (see Fig. 1 and Table 1). These studies used a variety of methods to assess neurobiological correlates (i.e., PET, MRI, fMRI, EEG, DTI) and S/R (e.g., self-transcendence, intrinsic religiosity) in relation to several aspects of mental health (e.g., depression, substance use, psychosis, and anxiety). Identified studies were assessed for quality based on statistical power as measured by post-hoc power analyses, the use of valid and reliable measures, and clinical relevance. Of the included studies, 15 were of moderate to high methodological quality and three were of low methodological quality.

Our review revealed important findings regarding relations among S/R, mental health, and neurobiology as well as important limitations in this area of study. Specifically, our review highlights the potentially protective role of religion against the development of depression. The reviewed studies indicate that religion is associated with a lower risk of depression, especially among those with familial risk (Oxhandler et al., 2018; Panier et al., 2020), and that religiosity is associated with several neurobiological correlates (e.g., greater cortical thickness (Miller et al., 2014; Liu et al., 2017), decreased DMN (Svob et al., 2016; Galanter et al., 2017), increased posterior EEG alpha at baseline (Tenke et al., 2013, 2017), slower ERP responsivity (Kayser et al., 2019)). These effects suggest that neural features may mediate the link between familial depression and incidence of depression (Miller et al., 2014; Svob et al., 2016; Tenke et al., 2013, 2017; Kayser et al., 2019; Li et al., 2019; Panier et al., 2020; Liu et al., 2017). Because seven of these studies utilize the same parent dataset these findings should be interpreted as tentative. As such, future research should directly test this hypothesis with additional datasets. Again, these findings must be taken in context with the limitations in this area. Research examining current depressive symptomatology was less clear. Two studies (Simmons et al., 2012; Miller and Barton, 2015) indicated that S/R may be associated with neurobiological correlates that are associated with decreased risk of depressive symptomatology, while the other two (Vlasova et al., 2018; Karlsson et al., 2011) did not reveal significant relations. Further research is needed to assess relations among familial risk for depression and current depressive symptomatology, S/R, and the brain. Additional research would allow for a systematic meta-analysis to further elucidate relationships.

This review also highlights important findings regarding the relationship across S/R, neurobiological correlates, and alcohol use (Galanter et al., 2017). Specifically, findings included that individuals in an experimental prayer group experienced less alcohol-craving when exposed to an alcohol-related image as well as increased activation in several brain regions (e.g., left-anterior middle frontal gyrus, left superior parietal lobule, bilateral precuneus, and bilateral posterior middle temporal gyrus) (Galanter et al., 2017). These results led the investigators to propose that prayer may reduce alcohol cravings and increase attention and control processes in the brain (Galanter et al., 2017). This finding expands what is known about prayer, S/R, and alcohol use and also serves as an example of rigorous research in the area of S/R, neurobiological correlates, and substance use. Researchers should consider using this study as a model for future research in this area.

With regards to anxiety and psychosis, however, it is difficult to draw meaningful conclusions based on the current data of S/R and neurobiology as it pertains to these aspects of mental health. Specifically, the two studies examining anxiety both reported null findings (Simmons et al., 2012; Baldwin et al., 2016). In addition, only one study examined (non-clinical) psychosis and the relationship with S/R and neurobiolgical correlates, and none have evaluated clinical psychotic symptoms (Pelletier-Baldelli et al., 2014). As such, much is left unknown about S/R, anxiety, psychosis, and the brain, and there is a clear need for greater research on this areas.

Regarding limitations of the current study, of the 18 articles included in this review, eight were based on the same data from the same parent study pertaining to family risk of depression. More important, *all* research reviewed regarding S/R, neurobiology, and familial risk for depression, came from the same single dataset (Miller et al., 2014; Svob et al., 2016; Tenke et al., 2013, 2017; Kayser et al., 2019; Li et al., 2019; Panier et al., 2020; Liu et al., 2017). As such, conclusions in this area must be interpreted with caution, since they may or may not be replicated by other laboratories and in other studies. Another significant and surprising limitation is that none of the studies included in this review examined clinical psychosis (Marriott et al., 2019), obsessive-compulsive disorder (Abramowitz and Buchholz, 2020), or hyper-religious mania (Ouwehand et al., 2020) despite prior research indicating that S/R is a contextual factor that can shape the course and presentation of these disorders. It is similarly surprising that only three neuroimaging studies examined S/R and alcohol/substance use, given the preponderance of research examining the efficacy of 12-step programs, which are spiritually-based and ubiquitous in the treatment of alcohol/substance misuse (Kelly and Eddie, 2020). An additional limitation observed in this review was the common use of single questions to assess S/R across studies. Future research should incorporate validated and more comprehensive measures of S/R to better assess relationships across S/R, mental health, and neurobiology.

It must be noted that the above limitations occur in the broader context of relatively limited funding being available to study the interplay of R/S, mental health, and neurobiology (Rim et al., 2019). A recent review of National Institute of Health funding in the United States revealed that the vast majority of research on S/R and health has been conducted in "healthy" populations, and nearly 60% considered S/R as a central focus for publications (Park et al., 2022). Because neurobiology research requires significant funding, there is a need for governmental agencies across the globe to recognize funding disparities in this area, in order to address the current limitations and gaps. In particular, further neuroimaging research is needed to examine relationships between S/R and depression, alcohol/substance use, anxiety, and psychosis using experimental research designs and multidimensional measurements of S/R.

## Author statement

DH Rosmarin lead the study as the primary investigator and oversaw the writing and editing of the manuscript.

CC Kaufman led the writing of the manuscript and also coordinated co-authors' opinions and feedback on the manuscript.

SS Friree Ford led the systematic search and review of articles included in the manuscript.

P Keshava supported the writing process as well as the collection and review of included articles in the manuscript.

M Drury participated in the writing and editing process.

S Minns supported the search for articles in the systematic review as well as the review of those articles.

C Marmarosh provided critical feedback regarding the search and review process for included articles as well as the conceptualization of results.

A Chowdhury provided critical feedback during the editing process and also aided in the conceptualization of the study results.

M Sacchet provided his expertise in the area of neuroscience to inform the approach to the study as well as the conceptualization of the study findings.

## Note

The authors have no conflicts of interest to disclose and jointly affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. Financial support was received from McLean Hospital

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## Declaration of competing interest

The authors have no conflicts of interest to disclose and jointly affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

## Appendix A. Search terms used for a systematic review of original papers examining mental health, spirituality, and neuroimaging

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| ((Neurobiology [MeSH Terms] OR Neuroimaging[MeSH Terms] OR Magnetic resonance imaging[MeSH Terms] OR Neurobiology OR EEG OR PET OR SPECT OR MRI OR fMRI OR neuroimaging OR imaging OR imagings OR Molecular Neurobiology OR Neurobiology, Molecular OR Cellular Neurobiology OR Neurobiology, Cellular OR Imaging, Brain OR Imaging, Magnetic Resonance OR Imaging, NMR OR Tomography, NMR OR Tomography, MR OR MR Tomography OR NMR Tomography OR Steady-State Free Precession MRI OR Steady State Free Precession MRI OR Zeugmatography OR Image, Magnetic Resonance OR Resonance Image, Magnetic OR MRI Scans OR MRI Scan OR Scan, MRI OR Scans, MRI OR Proton Spin Tomography OR fMRI OR MRI, Functional OR Functional MRI OR Functional MRIs OR Magnetic Resonance Imaging, Functional OR neurobiological factor OR neurobiological factors OR neuro-imaging OR magnetic resonance tomography OR neural activity) AND (spirituality[MeSh Terms] OR religion[MeSh Terms] OR religion and psychology[MeSh Terms] OR spirituality OR Religion OR Spiritualities OR Religions OR Psychology, Religion OR Religion, Psychology OR Psychology and Religion OR religion and psychology)) AND (Mental Health[Mesh Terms] OR Behavioral Symptoms [Mesh Terms] OR Mental Disorders[Mesh Terms] OR Psychotherapy[Mesh Terms] OR Psychiatric Somatic Therapies [Mesh Terms] OR Impulsive Behavior[Mesh Terms] OR Substance-related disorders[Mesh Terms] OR Behavior, Addictive[Mesh terms] OR Mental OR Behavioral Symptom OR Behavioral symptoms OR Symptom, Behavioral OR Symptoms, Behavioral OR Psychiatric OR Behavior Disorders OR Psychotherapies OR Psychotherapeutic OR psychotherapy OR Behavior, Impulsive OR Behaviors, Impulsive OR Impulsive Behaviors OR Impulsivity OR Impulsivities OR psychological well being OR psychological wellbeing OR Psychological well-being OR mentally ill OR neurodevelopmental disorder OR neurodevelopmental disorders OR neuropsychiatric disease OR neuropsychiatric diseases OR neuropsychiatric disorder OR neuropsychiatric disorders OR psychic disease OR psychic disorder OR psychic disturbance OR psychologic disorder OR psychologic disturbance OR psychological disorder OR psychological disturbance OR psychopathology OR multiple psychotherapy OR psychotherapeutic processes OR psychotherapeutic training OR psychotherapy, multiple OR socioenvironmental therapy OR Substance Use OR Substance Uses OR Use, Substance OR Drug Abuse OR Abuse, Drug OR Drug Dependence OR Dependence, Drug OR Drug Addiction OR Addiction, Drug OR Drug Use Disorders OR Disorder, Drug Use OR Drug Use Disorder OR "Substance Induced Organic Mental Disorders" OR Substance Abuse OR Abuse, Substance OR Substance Abuses OR Substance Dependence OR Dependence, Substance OR Substance Addiction OR Addiction, Substance OR Chemical Dependence OR Dependence, Chemical OR Prescription Drug Abuse OR Abuse, Prescription Drug OR Drug Abuse, Prescription OR Drug Habituation OR Substance related disorder OR Behavior, addictive OR Addictive Behavior OR Addictive Behaviors OR Behaviors, Addictive OR addict OR drug addict OR drug dependency OR drug facilitation OR physical dependence OR substance dependency OR toxicomania OR toxicomanias OR toxicomanie) |
| EMBASE |
| ('Neurobiology'/exp/mj OR 'Neuroimaging'/exp/mj OR 'Nuclear magnetic resonance imaging'/exp/mj OR 'Neurobiology':ti,ab,kw OR 'EEG':ti,ab,kw OR 'PET':ti,ab,kw OR 'SPECT':ti,ab,kw OR 'MRI':ti,ab,kw OR 'fMRI':ti,ab, kw OR 'neuroimaging':ti,ab,kw OR 'imaging':ti,ab,kw OR 'imagings':ti,ab,kw OR 'Molecular Neurobiology':ti,ab,kw OR 'Neurobiology, Molecular':ti,ab,kw OR 'Cellular Neurobiology':ti,ab,kw OR 'Neurobiology, Cellular':ti,ab,kw OR 'Imaging, Brain':ti,ab,kw OR 'Imaging, Magnetic Resonance':ti,ab,kw OR 'Imaging, NMR':ti,ab,kw OR 'Tomography, NMR':ti,ab,kw OR 'Tomography, MR':ti,ab,kw OR 'MR Tomography':ti,ab,kw OR 'NMR Tomography':ti, ab,kw OR 'Steady-State Free Precession MRI':ti,ab,kw OR 'Steady State Free Precession MRI':ti,ab,kw OR 'Zeugmatography':ti,ab,kw OR 'Image, Magnetic Resonance':ti,ab,kw OR 'Resonance Image, Magnetic':ti,ab,kw OR 'MRI Scans':ti,ab,kw OR 'MRI Scan':ti,ab,kw OR 'Scan, MRI':ti,ab,kw OR 'Scans, MRI':ti,ab,kw OR 'Proton Spin Tomography':ti,ab,kw OR 'fMRI':ti,ab,kw OR 'MRI, Functional':ti,ab,kw OR 'Functional MRI':ti,ab,kw OR 'Functional MRIs':ti,ab,kw OR 'Magnetic Resonance Imaging, Functional':ti,ab,kw OR 'neurobiological factor':ti,ab,kw OR 'neurobiological factors':ti,ab,kw OR 'neuro-imaging':ti,ab,kw OR 'magnetic resonance tomography':ti,ab,kw OR 'neural activity':ti,ab,kw) AND ('religion'/exp/mj OR 'spirituality':ti,ab,kw OR 'Religion':ti,ab,kw OR 'Spiritualities':ti, ab,kw OR 'Religions':ti,ab,kw OR 'Psychology, Religion':ti,ab,kw OR 'Religion, Psychology':ti,ab,kw OR 'Psychology and Religion':ti,ab,kw OR 'religion and psychology':ti,ab,kw) AND ('Psychological well-being'/exp/mj OR 'Mental disease'/exp/mj OR 'Psychotherapy'/exp/mj OR 'Psychiatric Treatment'/exp/mj OR 'Drug Dependence'/exp/mj OR 'Mental':ti,ab,kw OR 'Behavioral Symptom':ti,ab,kw OR 'Behavioral symptoms':ti,ab,kw OR 'Symptom, Behavioral':ti, ab,kw OR 'Symptoms, Behavioral':ti,ab,kw OR 'Psychiatric':ti,ab,kw OR 'Behavior Disorders':ti,ab,kw OR 'Psychotherapies':ti,ab,kw OR 'Psychotherapeutic':ti,ab,kw OR 'psychotherapy':ti,ab,kw OR 'Behavior, Impulsive':ti, ab,kw OR 'Behaviors, Impulsive':ti,ab,kw OR 'Impulsive Behaviors':ti,ab,kw OR 'Impulsivity':ti,ab,kw OR 'Impulsivities':ti,ab,kw OR 'psychological well being':ti,ab,kw OR 'psychological wellbeing':ti,ab,kw OR 'Psychological well-being':ti,ab,kw OR 'mentally ill':ti,ab,kw OR 'neurodevelopmental disorder':ti,ab,kw OR 'neurodevelopmental disorders':ti,ab,kw OR 'neuropsychiatric disease':ti,ab,kw OR 'neuropsychiatric diseases':ti,ab,kw OR 'neuropsychiatric disorder':ti,ab,kw OR 'neuropsychiatric disorders':ti,ab,kw OR 'psychic disease':ti,ab,kw OR 'psychic disorder':ti,ab,kw OR 'psychic disturbance':ti,ab,kw OR 'psychologic disorder':ti,ab,kw OR 'psychologic disturbance':ti,ab,kw OR 'psychological disorder':ti,ab,kw OR 'psychological disturbance':ti,ab,kw OR 'psychopathology':ti,ab,kw OR 'holistic psychotherapy':ti,ab,kw OR 'multiple psychotherapy':ti,ab,kw OR 'psychotherapeutic processes':ti,ab,kw OR 'psychotherapeutic training':ti,ab,kw OR 'psychotherapy multiple':ti,ab,kw OR 'socioenvironmental therapy':ti,ab,kw OR 'Substance Use':ti,ab,kw OR 'Substance Uses':ti,ab,kw OR 'Use, Substance':ti,ab,kw OR 'Drug Abuse':ti,ab,kw OR 'Abuse, Drug':ti,ab,kw OR 'Drug Dependence':ti,ab,kw OR 'Dependence, Drug':ti,ab,kw OR 'Drug Addiction':ti,ab,kw OR 'Addiction, Drug':ti,ab,kw OR 'Drug Use Disorders':ti,ab,kw OR 'Disorder, Drug Use':ti,ab,kw OR 'Drug Use |

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| Disorder':ti,ab,kw OR 'Substance Induced Organic Mental Disorders':ti,ab,kw OR 'Substance Abuse':ti,ab,kw OR 'Abuse, Substance':ti,ab,kw OR 'Substance Abuses':ti,ab,kw OR 'Substance Dependence':ti,ab,kw OR 'Dependence, Substance':ti,ab,kw OR 'Substance Addiction':ti,ab,kw OR 'Addiction, Substance':ti,ab,kw OR 'Chemical Dependence': ti,ab,kw OR 'Dependence, Chemical':ti,ab,kw OR 'Prescription Drug Abuse':ti,ab,kw OR 'Abuse, Prescription Drug':ti, ab,kw OR 'Drug Abuse, Prescription':ti,ab,kw OR 'Drug Habituation':ti,ab,kw OR 'Substance related disorder':ti,ab,kw OR 'Behavior, addictive':ti,ab,kw OR 'Addictive Behavior':ti,ab,kw OR 'Addictive Behaviors':ti,ab,kw OR 'Behaviors, Addictive':ti,ab,kw OR 'addict':ti,ab,kw OR 'drug addict':ti,ab,kw OR 'drug dependency':ti,ab,kw OR 'drug facilitation': ti,ab,kw OR 'physical dependence':ti,ab,kw OR 'substance dependency':ti,ab,kw OR 'toxicomania':ti,ab,kw OR 'toxicomanias':ti,ab,kw OR 'toxicomanie':ti,ab,kw) |
| PsycINFO and CINAHL via EBSCO |
| ((MM "Neurobiology" OR MM "Cellular Neuroscience" OR MM "Developmental Neuroscience" OR MM "Neuroimaging" OR MM "Encephalography" OR MM "Magnetic Resonance Imaging" OR MM "Roentgenography" OR MM "Stereotaxic Atlas" OR MM "Tomography") OR TI (Neurobiology OR EEG OR PET OR SPECT OR MRI OR fMRI OR neuroimaging OR imaging OR imagings OR Molecular Neurobiology OR Neurobiology, Molecular OR Cellular Neurobiology OR Neurobiology, Cellular OR Imaging, Brain OR Imaging, Magnetic Resonance OR Imaging, NMR OR Tomography, NMR OR Tomography, MR OR MR Tomography OR NMR Tomography OR Steady-State Free Precession MRI OR Steady State Free Precession MRI OR Zeugmatography OR Image, Magnetic Resonance OR Resonance Image, Magnetic OR MRI Scans OR MRI Scan OR Scan, MRI OR Scans, MRI OR Proton Spin Tomography OR fMRI OR MRI, Functional OR Functional MRI OR Functional MRIs OR Magnetic Resonance Imaging, Functional OR neurobiological factor OR neurobiological factors OR neuro-imaging OR magnetic resonance tomography OR neural activity) OR AB (Neurobiology OR EEG OR PET OR SPECT OR MRI OR fMRI OR neuroimaging OR imaging OR imagings OR Molecular Neurobiology OR Neurobiology, Molecular OR Cellular Neurobiology OR Neurobiology, Cellular OR Imaging, Brain OR Imaging, Magnetic Resonance OR Imaging, NMR OR Tomography, NMR OR Tomography, MR OR MR Tomography OR NMR Tomography OR Steady-State Free Precession MRI OR Steady State Free Precession MRI OR Zeugmatography OR Image, Magnetic Resonance OR Resonance Image, Magnetic OR MRI Scans OR MRI Scan OR Scan, MRI OR Scans, MRI OR Proton Spin Tomography OR fMRI OR MRI, Functional OR Functional MRI OR Functional MRIs OR Magnetic Resonance Imaging, Functional OR neurobiological factor OR neurobiological factors OR neuro-imaging OR magnetic resonance tomography OR neural activity) OR KW (Neurobiology OR EEG OR PET OR SPECT OR MRI OR fMRI OR neuroimaging OR imaging OR imagings OR Molecular Neurobiology OR Neurobiology, Molecular OR Cellular Neurobiology OR Neurobiology, Cellular OR Imaging, Brain OR Imaging, Magnetic Resonance OR Imaging, NMR OR Tomography, NMR OR Tomography, MR OR MR Tomography OR NMR Tomography OR Steady-State Free Precession MRI OR Steady State Free Precession MRI OR Zeugmatography OR Image, Magnetic Resonance OR Resonance Image, Magnetic OR MRI Scans OR MRI Scan OR Scan, MRI OR Scans, MRI OR Proton Spin Tomography OR fMRI OR MRI, Functional OR Functional MRI OR Functional MRIs OR Magnetic Resonance Imaging, Functional OR neurobiological factor OR neurobiological factors OR neuro-imaging OR magnetic resonance tomography OR neural activity)) AND ((MM "Spirituality" OR MM "Spiritual Well Being" OR MM "Religion" OR MM "Religiosity" OR MM "Religious Beliefs" OR MM "Religious Practices") OR TI (spirituality OR Religion OR Spiritualities OR Religions OR Psychology, Religion OR Religion, Psychology OR Psychology and Religion OR religion and psychology) OR AB (spirituality OR Religion OR Spiritualities OR Religions OR Psychology, Religion OR Religion, Psychology OR Psychology and Religion OR religion and psychology) OR KW (spirituality OR Religion OR Spiritualities OR Religions OR Psychology, Religion OR Religion, Psychology OR Psychology and Religion OR religion and psychology)) |
| Web of Science |
| TS=(Neurobiology OR "Cellular Neuroscience" OR "Developmental Neuroscience" OR Neuroimaging OR Encephalography OR "Magnetic Resonance Imaging" OR Roentgenography OR "Stereotaxic Atlas" OR Tomography OR EEG OR PET OR SPECT OR MRI OR fMRI OR imaging OR imagings OR "Molecular Neurobiology" OR "Cellular Neurobiology" OR "MR Tomography" OR "NMR Tomography" OR "Steady-State Free Precession MRI" OR "Steady State Free Precession MRI" OR Zeugmatography OR "MRI Scans" OR "MRI Scan" OR "Proton Spin Tomography" OR fMRI OR "Functional MRI" OR "Functional MRIs" OR "neurobiological factor" OR "neurobiological factors" OR "neuro-imaging" OR "magnetic resonance tomography" OR "neural activity") AND TS=(Spirituality OR "Spiritual Well Being" OR Religion OR Religiosity OR "Religious Beliefs" OR "Religious Practices" OR Spiritualities OR Religions OR "Psychology and Religion" OR "religion and psychology") AND TS=("Mental Health" OR "Behavioral Symptoms" OR "Mental Disorders" OR Psychotherapy OR "Psychiatric Somatic Therapies" OR "Impulsive Behavior" OR "Substance-related disorders" OR "Addictive Behavior" OR Mental OR "Behavioral Symptom" OR Psychiatric OR "Behavior Disorders" OR Psychotherapies OR Psychotherapeutic OR "Impulsive Behaviors" OR Impulsivity OR Impulsivities OR "psychological well being" OR "psychological wellbeing" OR "Psychological well-being" OR "mentally ill" OR "neurodevelopmental disorder" OR "neurodevelopmental disorders" OR "neuropsychiatric disease" OR "neuropsychiatric diseases" OR "neuropsychiatric disorder" OR "neuropsychiatric disorders" OR "psychic disease" OR "psychic disorder" OR "psychic disturbance" OR "psychologic disorder" OR "psychologic disturbance" OR "psychological disorder" OR "psychological disturbance" OR psychopathology OR "multiple psychotherapy" OR "psychotherapeutic processes" OR "psychotherapeutic training" OR "socioenvironmental therapy" OR "Substance Use" OR "Substance Uses" OR "Drug Abuse" OR "Drug Dependence" OR "Drug Addiction" OR "Drug Use Disorders" OR "Drug Use Disorder" OR "Substance Induced Organic Mental Disorders" OR "Substance Abuse" OR "Substance Abuses" OR "Substance Dependence" OR "Substance Addiction" OR "Chemical Dependence" OR "Prescription Drug Abuse" OR "Drug Habituation" OR "Substance related disorder" OR "Addictive Behaviors" OR addict OR "drug addict" OR "drug dependency" OR "drug facilitation" OR "physical dependence" OR "substance dependency" OR toxicomania OR toxicomanias OR toxicomanie) |

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