Research Article

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Journal of Neurology and Neuroscience
ISSN 2171-6625

2021
Vol.12 No. 9:9801

Religiosity and Depression: Does a Belief System Play a Neuroprotective Role?

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Received date: July 28, 2021; **Accepted date:** October 11, 2021; **Published date:** October 21, 2021

Citation: Song J (2021) Religiosity and Depression: Does a Belief System Play a Neuroprotective Role?, J Neurol Neurosci, Vol: 12 No: 9

Abstract

Depression is a prevalent and burdening disease that brings serious challenges to individuals who suffer from it. Religion is a unified system of belief, practices, and the community which surrounds the belief. The neuroscience of depression has received more attention in recent years, yet how a belief system influences depression is poorly studied. To examine whether religion is neuroprotective against depression, this paper investigates the neurophysiology, neuroanatomy, and neuroendocrinology associated with religiosity, and their impact the neuropathology of depression. After analyzing studies conducted by other researchers, the main results are as follows: High personal importance of religion correlates with prominent posterior EEG alpha, which counters a genetic predisposition to depression and predicts a better prognosis. High personal importance of religion increases cortical thickness where thinner cortices predict a high risk of developing depression. Meditation increases the extracellular dopamine level, which counters the dopamine deficit exhibited by the depression-predisposed population. Religiosity has a nuanced relationship with hippocampal volume in elder populations, but hippocampal atrophy is less significant in people with a religious belief compared to areligious controls. The results indicate a neuroprotective effect of high religiosity against the onset of depression. Future research should specify what aspects of a belief system confer resilience to depression, which has potential clinical implications.

Key Words: Depression; religiosity; multidimensional; cortic al thickness; EEG alpha; monoamine neurotransmitters; hippocampal volume.

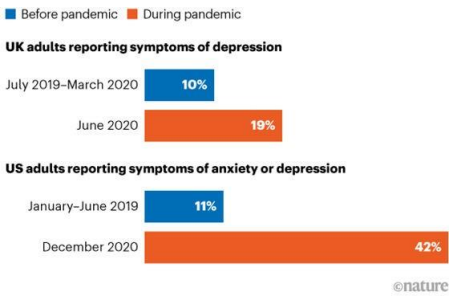
Introduction

Depression

Major depressive disorder (MDD) is an affective disorder that severely undermines one's psychosocial functioning and diminishes quality of life. MDD is characterized by feelings of unpleasantness, anhedonia, helplessness, and despair. Symptoms include weight changes, sleep disturbances, psychomotor retardation, fatigue, and decreased concentration (Diagnostic and Statistical Manual of Mental Disorders).

The WHO predicted that MDD would be the leading cause of burden and disability worldwide by 2030, before cancer and cardiovascular diseases (WHO 2008). Pre-COVID lifetime risk of depression was 15-18%, meaning one in five people experienced at least one MDD episode (Bromet). Multiple studies show that depression is about twice as common in women than in men, and the gender gap is linked to biological and psychological sex differences as well as environmental factors (Kuehner).

Figure1: "The percentage of people experiencing symptoms of depression and anxiety has surged amid the COVID-19 pandemic, data from nationally representative surveys show" (Abbott).



Because people have been subject to considerable degrees of worry, fear, and uncertainty, the COVID-19 pandemic has induced a mental health crisis, with rising depression rates globally. National surveys conducted by National Statistics (UK data) and the Centers for Disease Control and Prevention (US data) show significant surges in the percentage of adults reporting symptoms of depression during COVID-19 compared to pre-COVID. Lifetime risk of depression is expected to rise accordingly. MDD has a high likelihood for recurrence, and the risk increases with every episode. A study in 2014 by Boschool et al. found that 27.8% of MDD patients develop chronic MDD, whereas 53% of patients with chronic MDD experience persisting symptoms [1].

Heritability plays a part in predicting the risk of depression, although its mechanisms and statistics are not well-understood. Scientists believe that in most cases of depression, around 50% is caused by genetics, and the other half is related to the environment. Monozygotic twins have identical genes, while dizygotic twins share 50% of their genes. For major depression, twin studies suggest a heritability of 40% to 50%, and family studies show having a first-degree relative with MDD can increase the risk of developing MDD 2 to 3 times compared to

an average person. Progress in locating and identifying genes is slow, but researchers agree unanimously on a genetic predisposition to depression.

The Brain, Neurons, and Circuits

Analyzing MDD through neuroscience might allow for a better understanding of the disease. The brain is the most complex organ of the human body. At the macro level, it is divided into three parts: the cerebrum, brainstem, and cerebellum. The cerebrum, the largest part of the brain, can be divided into left and right hemispheres. The two hemispheres are connected by a "bridge" formed by bundles of nerve fibers called the corpus callosum, allowing the two sides of the brain to interact with each other. Each hemisphere can be divided into four lobes, each of which performs different functions. In this study, I focus on the brain as a whole, as well as the parts associated with MDD. I then investigate how a belief system influences the neurophysiology, neuroanatomy, and neuroendocrinology of the human brain.

To examine religion's effects on the depression-predisposed brain, the effects of depression on the brain must first be identified. Several dimensions of the nervous system are closely related to risk of depression [2,3].

The Neurophysiology of MDD – posterior EEG alpha

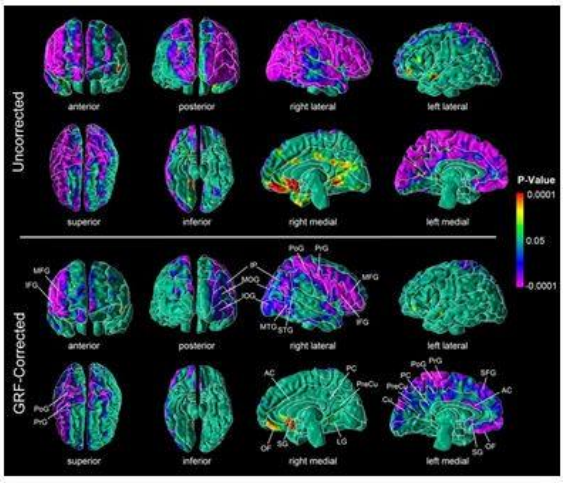
Electroencephalogram (EEG) alpha (also referred to as alpha, alpha power, or EEG alpha power) is a brain wave associated with relaxed waking states and is maximal with eyes closed (Bear). Its power has been associated with both the risk and the prognosis of MDD. As early as 1989, Pollock & Schneider suggested that alpha power could be an indication of familial risk for depression from clinical observations. Bruder further observed that offspring with two parents with MDD showed greater posterior alpha (the alpha wave obtained in posterior regions of the brain) compared to those with one or no depressed parent. In 2008, the same researchers found that MDD patients who responded to serotonin reuptake inhibitors (SSRIs, a popular medication for MDD) had greater alpha power compared to patients who do not respond to them, and the difference persisted after treatment. These all point towards a prominent role played by alpha power in the diagnosis and prediction of depression.

Another prominent finding in EEG alpha research is its association with personal religiosity. Tenke obtained clinical evaluations and self-reports of religiosity from 52 participants and did so again at a ten-year follow-up. Researchers evaluated EEG alpha at the T10 and found participants who rated religiosity high at both times exhibited greater alpha compared to participants with other religiosity ratings. An individual's posterior alpha is a relatively stable trait, with little variation across long time intervals in adults, and is independent of the onset and treatment of depression (Pollock & Schneider). If Pollock & Schneider's finding is valid, alpha power could be a life-long predictor of depression risks, with low alpha indicating .

The Neuroanatomy of MDD – Structural Changes

Cortical thickness is the distance between points on the pial and white matter boundaries of the neocortex. It measures the thickness of the human cerebral cortex and enables the diagnosis and study of the cortical mantle in various states (Abe). Cortical thickness is determined by the number and size of neurons, extent of myelination, and their arrangements (Narr; Seldon). Comparisons of cortical thickness between MDD patients and healthy controls demonstrate prominent differences, as studied by Peterson: 131 individuals were scanned, 66 (12 children, 54 adults) in the high-risk group and 65 in the low-risk group (31 children, 34 adults). The risk groups were established based on history of family depression: for example, if one parent of the participant experienced MDD, the participant was assigned to the high-risk group; those with non-depressed parents were assigned to the low-risk group. Longitudinal assessment in this sample and 2-generation studies demonstrated that the high-risk group had a greater frequency of lifetime MDD (n = 37, 56%) compared to the low-risk group (n = 15, 23%) ($\chi 2 = 13.54$, df = 1, P = 0.0002). At the time of the scan, the high-risk group had significantly more current MDD than the low-risk group (high-risk group: n = 16, 25%; low-risk group: n = 7, 11%; $\chi 2 = 4.28$, df = 1, P < 0.05).

Figure2: Maps of group differences in cortical thickness (Peterson). Thinner cortices are represented by cooler colors (blue and purple). The color bar shows the color-coding of p-value. The upper map shows thinner cortices (P < 0.05) without statistical corrections. The lower map shows P < 0.05 after correcting the data (using the theory of Gaussian random fields (GRF) on a 2D manifold). Cu, cuneus; IF, inferior frontal gyrus; IOG, inferior occipital gyrus; IP, inferior parietal lobule; LG, lingual gyrus; MGF, middle frontal gyrus; MOG, middle occipital gyrus; MTG, middle temporal gyrus; OF, orbitofrontal cortex; PC, posterior cingulate; PoG, postcentral gyrus; PreCu, precuneus; PrG, precentral gyrus; SG, subgenual cortex; STG, superior temporal[4,5].



Using MRI scanning (see methods section), researchers found that the high-risk group exhibited statistically significant thinning in the lateral right hemisphere, including in the inferior and middle frontal gyri, somatosensory and motor cortices, dorsal and inferior parietal regions, the inferior occipital gyrus, and the

posterior temporal cortex (See Fig 3, Peterson). The high-risk MDD group exhibited an 0.87 mm reduction on average in the lateral aspect of the right hemisphere (range 0.55-1.36 mm), which is 28% less than the average cortical thickness of a healthy control (3 mm) (Peterson). This reduction is prominent enough to rival the magnitude of thinning found in cases of schizophrenia (Narr) and Alzheimer's disease (Im). Additional thinning was detected on the left hemisphere, including in the precuneus, the cuneus, the subgenual cortex, and the anterior and posterior cingulate cortices (See Fig 3, Peterson). These findings were consistent among adults and children. These results shown that significant cortical thinning is present in biological descendants of people with MDD regardless of whether the descendant experienced a MDD episode. Thinning in the above cortical mantle areas is symptomatic of a familial vulnerability for developing MDD [6-8].

Peterson et al.'s research yielded three prominent findings

- individuals with symptoms of MDD had the most extensive cortical thinning in both the posterior right hemisphere and the posterior left hemisphere;
- cortical thinning contributed prominently to both depression and anxiety symptoms;
- cortical thinning contributed to MDD symptoms in all groups, not confined to subjects with familial risk of depression.

In later sections, I will relate the above findings to studies which draw correlations between religiosity and depression.

The Neuroanatomy of MDD – Functional Changes

Monoamine neurotransmitters (serotonin, noradrenaline, and dopamine) are believed to be the biological base of affective disorders, which include bipolar disorder and major depression (Malhi and Mann). In the 1960s, medical workers found that the drug reserpine, which depletes central catecholamines and serotonin as a side effect, caused 20% of patients to develop psychotic depression (Schildkraut). They also found that drugs inhibiting monoamine oxidase caused significant elevation of mood when treating tuberculosis patients. These observations led researchers to develop the monoamine neurotransmitter hypothesis: depression is caused by a deficit of monoamine neurotransmitters in the brain. Although this theory is widely accepted, it fails to account for individual variances of depressive symptoms and episodes as well as why different patients respond differently to antidepressants (Malhi and Mann). In "The Chemistry of Religiosity," McNamara reported the association between prefrontal functions and changes in religious behavior, as well as the positive correlation between changes in dopamine levels and variations in religiosity. It is worth noticing that significant loss of religiosity usually accompanies Parkinson's disease, a nervous system disorder caused by loss of dopamine activity in the CNS. McNamara et al. thus predicted the supporting role of dopamine in certain aspects of religiosity [12,13].

The Neuroendocrinology of MDD – the HPA Axis

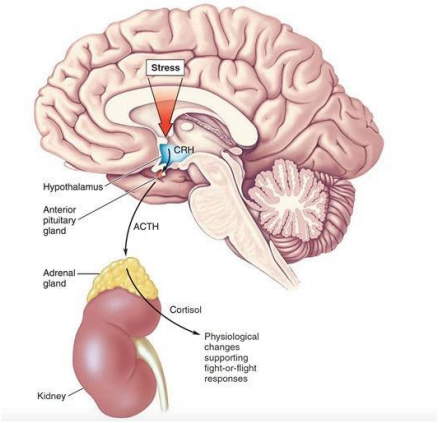


Figure3: The HPA Axis (Bear et al. 2007)

The hypothalamic-pituitary-adrenal (HPA) axis regulates stress response in the human body. Studies over the past decades concluded that HPA axis hyperactivity is the most consistent biological finding in the neuropathology of MDD (Pariante and Lightman). When the body psychologically interprets a threatening or stressful situation, the hypothalamus releases a chemical messenger: corticotropin-releasing hormone (CRH). CRH travels to the pituitary gland, where it triggers adrenocorticotropic hormone (ACTH) release. ACTH travels to the adrenal gland atop the kidney via the bloodstream. The adrenal gland then releases the stress hormone cortisol which quickens heart rate and prepares the body for fight-or-flight responses[9-11].

Much can be learned about depression by understanding the HPA axis. Research demonstrates when CRH is overexpressed in genetically engineered mice, releasing high amounts of cortisol, the animals display increased anxiety-like symptoms (Bear,). Cortisol has a negative feedback mechanism on the HPA axis to ensure the body does not secrete excessive amounts of cortisol. An important part of this feedback loop is the hippocampus, the brain area which has the highest concentration of cortisol receptors and is most sensitive to adrenocortical steroid levels. Hippocampal activation suppresses CRH release, acting as the feedback regulator of the HPA axis to terminate cortisol release if adrenocortical steroid is overproduced. However, there is a limit to hippocampal regulation. Long-term exposure to cortisol can cause hippocampal dendrites to whither, and a few weeks later these neurons die (Sapolsky). This results in impaired hippocampal function and gradual loss of sensibility to CRH levels. A vicious cycle persists: unregulated CRH secretion leads to prolonged cortisol exposure, resulting in more hippocampal damage. Long-term memory formation, one neurocognitive role of the hippocampus, is impaired during prolonged stress (Sapolsky et al. 1986). Depressed patients experience up to 20% of hippocampal atrophy, which explains some well-documented cognitive impairments of depression (Sapolsky).

Research by Pariante and Lightman concludes that HPA axis hyperactivity is not a consequence of depression, but rather a risk factor predisposing one to develop depression because the activities of the axis are closely related to genetic liability and molecular transformations induced by early life experiences. In

2001, Sanchez, Ladd, and Plotsky performed laboratory experiments manipulating the duration, frequency, and developmental stages of separation between non-human primates and their mothers. Their animal experiments suggested early maternal or social deprivation increases fearfulness, anxiety, social dysfunction, and sexual dysfunction long term. Neonate rats also exhibited reduced preference for sucrose, which is a sign of anhedonia in depressive states. Furthermore, rats with neonatal maternal separation demonstrated dramatic increases in adult HPA axis activity, supporting the influence of early life trauma on lifetime HPA axis hyperactivity [14,15].

Religion

Overview

Religion is often defined as the belief or worship in the supernatural. Durkheim (1976, 47) defined religion as a unified system of belief, practices, and the moral community which forms around the belief. By this definition, religion is not simply an inner belief or spiritual pursuit. Instead, it is a belief system that performs a cultural role of a community with unique sets of practices. In 2015, the Pew Research Center conducted a demographic projection of religion and concluded that 84% of the world population affiliates with some kind of religion or belief.

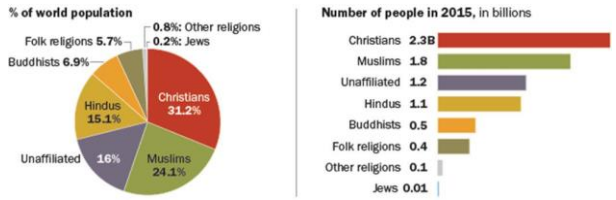


Figure4: Demographic Projection of Religion (Pew Research Center 2015).

With the large body of religious affiliation, examining how and why religion influences MDD is an important task. Research has shown that the extent of believers' devotion and religion's importance to them could differentiate the effects of religion on the brain. To reduce variability in our results and better identify the factors, I use the term religiosity to designate the quality and state of being religious and/or spiritual. High religiosity would suggest high personal importance of religion/spirituality. Common religious practices include worship service attendance, participation in scripture study or prayer groups, and private devotions including meditation, praying, and scripture reading outside of religious services (Pew Research Center).

Among all religious practices, research over the past decades has consistently shown a myriad of psychological and physiological benefits of meditation. Psychological benefits include stress reduction (Arias; Horowitz), decreased anxiety (Arias.; Orme-Johnson and Barnes), reduced pain (Horowitz; Orme-Johnson), decreased depression (Arias), and improved memory (Horowitz). Physiological benefits include reduced cortisol (Lau), reduced epinephrine (Infante), and increased blood flow in the anterior and frontal cingulate cortices of the brain (Wang; Javning). Although meditation can be a secular practice, religious people meditate more frequently. In 2014, 40% of Americans with a religious affiliation report meditating weekly or more often, and the highest percentage occurs among US Buddhists (66%). The percentage of believers who meditate weekly is more than two times the percentage of meditating atheists (19%) (Pew Research Center). Although meditation is not unique to religious groups, I thus conclude that the health benefits derived from meditation give more advantages to the religious population.

The Neuroscience of Religion

Bruce and Richie noted that neuroscience has not adequately examined how religiosity affects brain function (Bruce and Ritchie). Past neuroscience research sought to avoid religiosity because religion focuses on the metaphysical (Bruce and Ritchie). However, pioneers have attempted to establish cognitive schemas and neural models for religious belief. Religious experiences are looked at as cognitive processes, mediated by a pre-established neural circuit (Azari). In multiple studies, religiosity has been documented to play a protective role against MDD (Azari; Harris; Lazar). Furthermore, the protective effect of religiosity correlates positively with religion's personal importance (Miller)[16].

Hypothesis

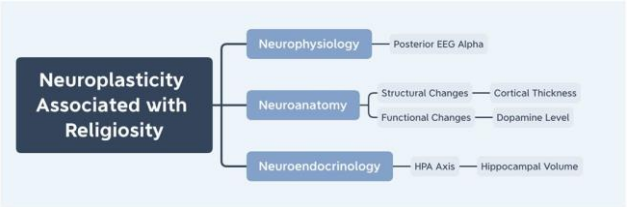


Figure5: Common factors of religiosity and depression discussed in this paper.

I hypothesize that a strong religious belief causes multidimensional changes in the brain that reduce the risk of developing MDD. These include neuroendocrinology, neuroanatomy, and neurophysiology.

- If people with high religiosity show greater posterior EEG alpha, I expect that a belief system decreases the risk of developing MDD.
- If high religiosity prevents the thinning of cortical regions where thinning suggests predisposition to MDD, I expect that a belief system plays a neuroprotective role against MDD via structural brain changes.
- If meditation keeps monoamine neurotransmitters in the synapses within a reasonable range, I expect that people who identify themselves as religious are less likely to develop MDD.
- If people with high religiosity have stabilized HPA axis function by preventing hippocampal volume decrease, I expect that a belief system plays a neuroprotective role against MDD via functional brain changes.
- If the four conditions above are substantiated, I conclude that a belief system (including the belief and common religious practices) is neuroprotective against MDD.

- With an ongoing global mental health crisis, investigating depression from multiple perspectives is crucial to developing treatments. I intend to connect the different aspects of the neuroplasticity of religion and the neuropathology of depression to determine common structures involved and discuss how the different factors interact to affect predispositions to MDD. Although the mechanisms of both depression and religion have been meticulously investigated by the scientific community, relatively little research has studied their relationship through the lens of neuroscience. This paper intends to fill this void and encourage more investigation on this topic.

Methods

PET

Positron emission tomography (PET) "is a type of nuclear medicine procedure that measures metabolic activity of the cells of body tissues" (Hopkinsmedicine). By bounding an unstable radioactive element to the target tissue, a scanning device can detect photons emitted by the element thus visualize biochemical changes in the body. In particular, carbon-11-raclopride (11C-raclopride) is a radioisotope which is used in cerebral PET scanning to measure cerebral D2 dopamine receptor binding.

MRI

Magnetic resonance imaging (MRI) is a brain imaging technique which yields detailed maps of the brain. In "Neuroanatomical Correlates of Religiosity and Spirituality," Miller performed a longitudinal study to assess religiosity and scanned 67 adult offspring of parents with one or more MDD onset (the descendants are high risk for MDD, or HR participants), and 36 adult offspring of healthy parents (low risk, or LR participants). Miller et al. acquired anatomical MRI data at T25. They co-registered each brain to a template brain selected by an expert and established point-by-point correspondence between the template brain and the brains of participants (with MRI data) with mathematical transformations and a warping algorithm. The use of a single brain as the template enables comparisons of cortical thickness across groups with different risks for depression and different levels of religiosity.

EEG

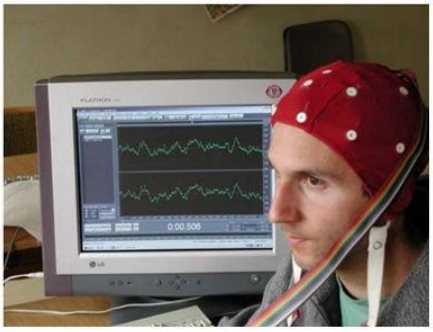


Figure6: Measuring with EEG (Cool).

An electroencephalogram (EEG) is a test that detects electrical activity in the brain by attaching small metal discs to participants' brains. Each disk is located near certain brain centers (e.g., center for rational activities, motivation, or emotional impulses). A unique label containing a letter and a number is assigned for each disk based on which lobe and hemisphere the electrode is located in (F-frontal, C-central, T-temporal, P-posterior, O-occipital; left-odd numbers, right-even numbers). Electrical signals received by electrodes will be gathered in a computer, where Fourier transform is applied and signals are converted to the frequency of brain waves.

Results

The Neurophysiology of the religious brain – Posterior EEG alpha

Tenke measured resting EEG while participants sat quietly for 2-minute periods (eyes-open and eyes-closed order counterbalanced across the sample). Thirteen disks were measured. EEG data were segmented into consecutive 1.28s epochs every .64 s (50% overlap), and epochs contaminated by blinks and eye movements were rejected.

Fifty-two participants were categorized into high and low risk for MDD based on family history. Religiosity was measured at T10 and T20. The classifier question of religiosity was "How important is religion or spirituality to you?" with options ranging from 1 ("not important at all") to 4 ("highly important"). Participants were dichotomized based on their responses, with 4 in the "Important" group, and all other responses in the "Not Important" group.

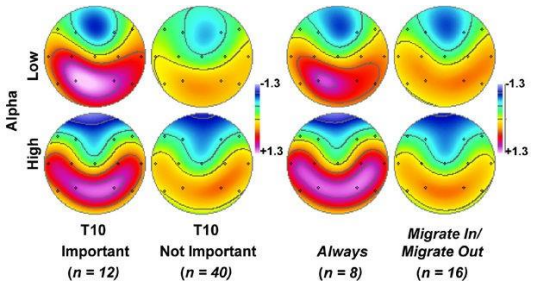


Figure7: Mean alpha factor score topographies across conditions (Tanke). See color bar for color coding: Low-frequency alpha is indicated by green and blue, and high-frequency alpha is indicated by red and purple. Migrate In/Migrate Out represents the group of participants that changed rating from 4 to below or vice versa. The corresponding number of participants for each category is labeled.

Researchers found that the 12 participants who reported important R/S at T10 exhibited significantly greater posterior alpha compared to the 40 who reported unimportant R/S (0.33 ± 0.63, $F[1,50] = 15.18$, $p < .001$). This difference in alpha is consistent in both low- and high-frequency conditions (see left, fig. 7). Furthermore, participants who rated religion as important in both assessments (Always, n=8) had significantly greater posterior alpha compared to those who rated religion as important in one out of two assessments (Migrate In/Migrate

Out, n=16). Figures on the right support greater alpha in participants who consistently rated R/S as important compared to those who changed their ratings (Always [n = 8]: 1.00 ± _0.65; Migrate Out/Migrate In [n = 16]: .39 ±0.71; F[1,22] = 4.21, p = . 05).

The Neuroanatomy of the Religious Brain

Structural Changes: Cortical thickness and Religiosity

Miller surveyed participants for their religiosity and categorized them into either high or low importance of religiosity/spirituality at T20 and T25 and performed MRI scans T25. They found that adults who reported high importance at T25 had thicker cortices in the left and right parietal and occipital regions, the medial frontal lobe of the right hemisphere, and the cuneous and precuneous in the left hemisphere (see Figure 10). Participants who consistently reported high importance at T20 and T25 had thicker cortices in the same regions compared to the template brain. This result is independent of familial risk, indicating that the thickening is the effect of high religiosity/spirituality alone.

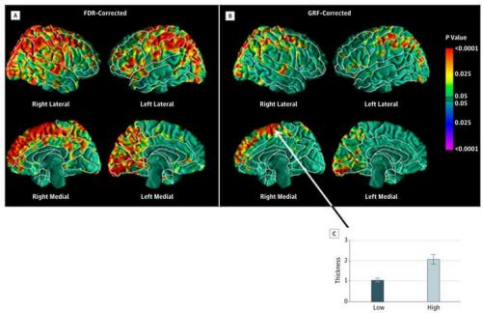


Figure8: Associations of religious and spiritual importance with cortical thickness (Miller).

In the study, associating cortical thickness with frequency of attendance of religious services yielded no statistically significant result. The bar chart in Figure 10 demonstrates the comparison of cortical thickness in the right medial view of the brain. Participants reporting high importance had twice the thickness of those reporting low importance.

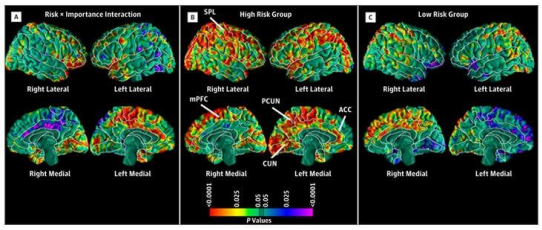


Figure9: Differing effects of religious and spiritual importance in the high- compared with the low-risk group.

The association between cortical thickness and religious importance is “strongest and spatially most extensive” in HR groups compared to LR groups. The first scan results on the left in Figure 11 show the interaction map of familial risk and religious importance at T25. “High-Risk Group” and “Low-Risk Group” in Figure 11 indicate that the effects of religious importance on cortical thickness are significantly more powerful in HR than LR participants, particularly across the orbital frontal cortex and the medial parts on both hemispheres. The same regions are known to be significantly thinner in those with familial risks for depression. Increased in thickness occurs in similar areas across HR and LR, supporting the conclusion that the structural changes accompanying high religiosity hold for the general population.

Functional Changes: Dopamine Level

Kjaer recruited eight healthy male meditation teachers from the Scandinavian Yoga and Meditation School, Copenhagen. Participants were experienced and practiced meditation daily for the past seven years. They had 11C-raclopride PET twice on different days. Each participant was guided by auditory CDs for 72 min, either following a standard meditation procedure or listening to speech with the same voice (control condition). 11C-raclopride was injected at 7 min after initiation, and participants were scanned for 85 min. After scanning the meditation group, participants completed a questionnaire on the quality of the meditation.

Researchers found a significant 7.9% decrease in binding potential in the ventral striatum during meditation compared to attention to speech. The decrease is evident in Figure 12. This decrease in binding potential represents increased endogenous dopamine release. Based on the results of microdialysis animal studies, the 7.9% decrease corresponds to an approximately 65% increase of extracellular dopamine release during meditation.

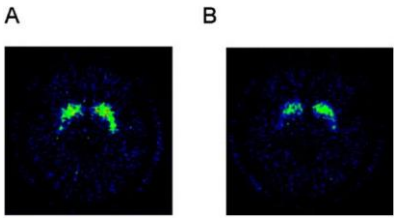


Figure10: 11C-raclopride binding potential images for one participant with the most significant decrease during meditation. A shows the speech condition, while B shows the meditation condition.

The Neuroendocrinology of Religiosity: Hippocampal volume

Owen et al. published a longitudinal study in 2011 which explored religious factors and hippocampal atrophy in elder populations. 268 participants aged 58 and over were recruited. Participants were assigned to two groups: those with at least one depressive episode according to DSM-IV criteria, and never-depressed participants. Exclusion criteria included other psychiatric illness, alcohol or drug dependence, dementia, and others. In this eleven-year longitudinal study, participants were scanned using MRI every two years, and religious, psychosocial, and demographic data were obtained at baseline and each consecutive year. Religious factors included frequency of public worship, frequency of private religious activity, religious

denomination, born-again status (a conversion experience), and life-changing religious experiences. Psychosocial and demographic covariates are presented in Image1.

	N (%) or Mean (SD)
Brain Volume	
Left hippocampus baseline (mL)	2.96 (0.43)
Left hippocampus final (mL)	2.97 (0.48)
Right hippocampus baseline (mL)	3.11 (0.43)
Right hippocampus final (mL)	3.06 (0.52)
Total cerebrum baseline (mL)	1151.66 (124.75)
Gender	
Female	182 (67.9%)
Male	86 (32.1%)
Age (years)	69.21 (6.44)
Race	
Asian	3 (1.1%)
Black	20 (7.5%)
Native American	1 (0.4%)
White	234 (87.3%)
Other	10 (3.7%)
Education (years)	14.64 (2.49)
Time in study (years)	4.49 (1.89)
Stress	4.88 (2.58)
Social Support	24.97 (3.51)
Religion	
Private practice	2.88 (1.89)
Public worship	2.97 (1.76)
Affiliation	
Non born-again Protestant	113 (42.2%)
Born-again Protestant	97 (36.2%)
Catholic	22 (8.2%)
Other religion	17 (6.3%)
No religion	19 (7.1%)
Religious experience	
Born-again (baseline)	97 (36.2%)
LCRE[a] (baseline)	13 (4.9%)
Born-again (new)	22 (8.2%)
LCRE[a] (new)	23 (8.6%)

[a]Life-changing Religious Experience.
doi:10.1371/journal.pone.0017006.t001

Image1: (left) Demographics, religious factors, covariates, and brain volume statistics (n=268).

	Left Hippocampus			Right Hippocampus		
	b	(SE)	β	*b*	(SE)	β
Intercept	0.45	(0.53)		0.48	(0.53)	
Religion/Spirituality						
Born-again[a] (new)	−0.05	(0.12)	0.03	−0.21	(0.12)	−0.12
LCRE[b] (baseline)	−0.45***	(0.12)	−0.22	−0.32	(0.13)	−0.16
LCRE[b] (new)	−0.01	(0.12)	−0.01	−0.15	(0.12)	−0.08
Born-again[a] (baseline)	−0.15*	(0.08)	−0.16	−0.15*	(0.08)	−0.16
Catholic	−0.22*	(0.11)	−0.13	−0.12	(0.11)	−0.07
Other	0.06	(0.12)	0.04	−0.05	(0.12)	−0.03
None	−0.28*	(0.12)	−0.13	−0.20	(0.12)	−0.10
Private practice	0.02	(0.02)	0.06	0.03	(0.02)	0.11
Public worship	−0.002	(0.02)	0.01	0.001	(0.02)	0.001
Covariates						
Depression status	−0.09	(0.09)	0.09	−0.08	(0.09)	0.08
Social support	0.01	(0.01)	0.09	0.01	(0.01)	0.09
Stress	0.01	(0.01)	0.03	0.003	(0.01)	0.02
Total brain size	0.0001	(0.001)	0.03	0.001	(0.001)	0.004
Age	−0.01*	(0.004)	−0.16	−0.01	(0.004)	−0.18
Duration in study	0.001	(0.02)	0.01	−0.01	(0.02)	0.02
Sex (female)	0.10	(0.08)	0.10	0.04	(0.08)	0.04
Race (White)	−0.004	(0.08)	−0.01	0.04	(0.08)	0.03
Education	−0.001	(0.01)	−0.01	0.004	(0.01)	0.02

*$p<.05$, ** $p<.01$,
***$p<.001$.
[a]Born-again labels refer to Protestants reporting born-again status.
[b]Life-changing Religious Experience.
doi:10.1371/journal.pone.0017006.t002

Image2: (right) Regression analysis of various factors and changes in hippocampal volume (n=268).(Owen)

Image2 reports longitudinal regression models of the connection between religious factors and changes in hippocampal volume. Life-changing religious experience at baseline was correlated with more atrophy in the left and right hippocampus (left: $b=-0.45$, $P<.001$; right: $b=-0.32$, $P=.012$). Protestants who reported born-again experiences at baseline had greater atrophy in the left and right hippocampus compared to non-born-again protestants (left: $b=-0.15$, $P=.046$; right: $b=-0.15$, $P=.050$). Catholic membership was associated with left hippocampal atrophy ($n=22$) ($b=-0.22$, $P=.046$). Excluding those with life-changing religious experiences at baseline, the most significant atrophy in the left hippocampus occurred in participants with no baseline religious group membership ($n=19$) ($b=-0.28$, $P=.046$). Left hippocampal volume decreased steadily with age ($b=-0.01$, $P<.05$). The influences of other covariates, such as depression status, social support, stress, sex, and race, were not statistically significant.

Discussion & Conclusion

This paper sought to investigate whether religiosity is neuroprotective against depression. I examined the three aspects of neuroplasticity associated with religiosity: neurophysiology, neuroanatomy, and neuroendocrinology. Critical reviews of four original research studies were performed, covering the topics of posterior EEG alpha, cortical thickness, dopamine level, and hippocampal volume. Each publication

related to one aspect of the neuroplasticity of the religious brain. I will relate each study to one condition in my hypothesis in the following analysis.

Research by Tenke concluded that high religiosity is associated with greater posterior EEG alpha. This agrees with my first condition under the hypothesis: the neurophysiology of a belief system protects against MDD by allowing higher frequency posterior alpha, thus decreasing the risk of MDD and predicting a better prognosis. A follow-up study by Tenke extended the time scale of their previous research by 10 years and replaced the 13 sites on the previous EEG machine with 72 sites. This new study found that individuals with higher religiosity had significantly greater posterior EEG alpha when measured at T30, and participants with consistent rating of high religious importance during four assessments (T10, T20, T25, T30) exhibited higher posterior alpha frequency compared to the "never important" or "migrate in" groups. These results all confirmed their previous findings.

Miller provided evidence for the countering effect of high religiosity against MDD on the cortical mantle: "Higher religiosity is associated with thicker cortices throughout the superior parietal and occipital lobes of the brain, where cortical thinning indicates a morphologic endophenotype of familial risk for MDD." Their results substantiate my second condition, providing evidence for a protective effect of religiosity via structural changes. Scientists generally agree that increased cortical thickness results in frequent use of certain circuits, which strengthens the connectivity and increases myelination and size of the cell body of the corresponding neurons on the cortical mantle. This suggests an enhanced neuronal activation in the orbital frontal cortex and the medial parts of the brain during religious activities or practices, which increases cortical thickness in these corresponding areas. Future research can address this prediction: Are certain pathways closely associated with religion in the occipital areas, and what are their functions? This might facilitate the location of the exact aspects of a belief system that play neuroprotective roles.

This study suggested notable differences between religious service attendance and religious importance. Miller et al. found that only 21 of the 49 participants reporting high attendance also reported high importance, indicating that church attendance has purposes other than cultivating personal religiosity. Surprisingly, in a previous study using the same sample, Kasen found a positive correlation between religious service attendance and risk of developing MDD once controlling for personal religious importance. This finding is quite counterintuitive. The evidence points toward the possibility of attending religious services to receive community support under emotional challenges.

Research by Miller and Tenke shares similar methodologies. Both studies categorized participants into high and low risk for MDD based on familial risk (lifetime risk predicted by parental MDD); participants were dichotomized based on self-reported ratings of religiosity/spirituality. One limitation for both studies is the homogeneousness of participants' religious denominations. The majority of their subjects were Catholic (48.5% in Miller et al.'s sample; 47 out of 67 in Tenke et al.'s sample at T10), with small proportions unaffiliated with an institutionalized religion. Buddhist/Hindu/Muslim participants were not present in their research samples. Due to an inadequate representation of different religious denominations, conclusions might be at best generalized to Catholic religiosity or religiosity under the United States demographics, but not universal religiosity. I suggest replication of the above experiments in more diverse religious samples.

Svob and Weissman did a follow-up study on cortical thickness and posterior EEG alpha. Over 35 years of studying three generations of families, Svob and Weissman applied MRI, EEG and DTI (Diffusion tensor imaging, a technique to detect brain microstructures) to study the effects of religiosity on people with high and low familial risk for MDD. Using the same cohort of participants as Peterson, their findings were consistent with both Peterson and Miller. The same regions present in 3.2.1 were thicker in high religiosity groups and the neuroprotective effect was confirmed. A follow-up study done 20 years later by Tenke reported high posterior alpha across time among participants who originally rated religious importance highly, even though some changed their ratings to low religiosity in later follow-ups. Interestingly, participants who rated religiosity as initially unimportant but important after mid-life did not attain high posterior alpha. As a result, Svob and Weissman proposed a potential "critical period" for attaining the protective effect of religion (against MDD). Their DTI study supported microstructural changes in the precuneus, frontal lobe, and temporal lobe brought by familial risk for MDD. These changes were less significant among participants with high religiosity. Researchers concluded that religiosity protects the brain from microstructural changes, thus conferring resilience to the genetically MDD-predisposed population.

My third condition is satisfied because meditation boosts dopamine levels, which provides the meditator with resilience against developing MDD according to the monoamine hypothesis of depression. In fact, the neuroanatomical benefit of meditation is far-reaching. Newberg and Iverson reviewed literature regarding neurophysiological and neurochemical mechanisms of meditation (see Table 3). They described an interactive system between different neurotransmitters and observed increased dopamine and serotonin release during meditation, which gives meditation an antidepressant effect (Mohandas E).

Neurochemical	*Observed change*	*CNS structure*
Arginine vasopressin	Increased	Supraoptic nucleus
GABA	Increased	Thalamus, other inhibitory structures
Melatonin	Increased	Pineal gland
Serotonin	Increased	Dorsal raphe
Cortisol	Decreased	Paraventricular nucleus
Norepinephrine	Decreased	Locus ceruleus
β -Endorphin	Rhythm changed; levels unaltered	Arcuate nucleus

Image3: Summary of Neurochemical changes in the CNS during meditation. (Monti and Newberg; originally from Newberg and Iversen)

On the molecular level, melatonin is found to increase during meditation. Melatonin, a hormone produced by the pineal gland at night, links with how the human body prepares for sleep. Studies have shown the positive correlation between melatonin level and happiness. Though some studies suggest melatonin as a significant treatment for MDD compared to a placebo, no conclusive evidence supports a therapeutic effect of melatonin against MDD (Hansen). Cortisol level decreases during meditation. As the neuromodulator of the HPA axis, cortisol level correlates with stress response. The decrease is consistent with less anxiety and stress reported by people in meditative states.

Apart from neurochemical changes, meditation brings long-lasting anatomical changes to the human brain. Meditation practitioners have increased grey matter volume, or cortical thickness, compared to non-practitioner controls (Lazar; **Hernández** ; Kang). PET and MRI data also suggested activation of the hippocampus during meditation compared to control states, and MRI data showed significantly larger volumes of the right hippocampus in long-term meditators (Luders).

The fourth condition in my hypothesis is partially substantiated. In the research by Owen, the extent of atrophy in elder people is greater in participants with no religious denomination and less among Catholics and born-again protestants. Curiously, the only religious group with more atrophy compared to the areligious participants is those who reported life-changing religious experiences. This points out a nuanced relationship between religiosity and hippocampal volume: a belief system does not necessarily prevent hippocampal atrophy, but certain religious denominations and experiences seem to slow down the atrophy compared to the areligious groups. With hippocampal atrophy being exhibited in patients with recurrent depression, certain religions or religious experiences are protective against the onset of MDD. This neuroprotective effect might not be conclusive, since researchers did not cross analyze the influence of high and low religiosity on hippocampal volume. Though Owen et al. did attempt to define high and low religiosity based on features like born-again experiences and life-changing religious experiences, this question might not be sufficiently representative to differentiate participants with high and low religiosity, and does not necessarily indicate religious importance. Since a lot of variations are present within the religious community, including personal importance of the belief and frequency of religious service attendance, defining high and low religiosity is utterly crucial. In addition, the study recruited only elder participants aged 58 and above, so the pattern might not be generalizable to the other age groups. As reported in the results, aging is also associated with more atrophy. Future research should address more demographic groups to substantiate the influence of religiosity (and/or religious denomination) on hippocampal volume. One limitation of this research is the failure to appreciate the multiple factors that influence hippocampal volume. For example, cardiorespiratory fitness, aerobic exercise, and socioeconomic status are significantly associated with hippocampal volume (Szabo, Firth, Yu). Due to the various cognitive functions which the hippocampus performs, it is not surprising to have so many factors involved. Owen et al. only controlled for psychosocial and demographic covariates like social support, stress, sex, and race. Studies on hippocampal volume should take into account other influential factors and control for them to reduce variations.

Previous studies have assessed religiosity based on a global assessment of religious importance. As McClintock et al. pointed out in their research, findings on religiosity and depression are commonly critiqued because the protective benefits of religiosity may pre-exist the clinical differences (Sloan). In other words, spirituality could be a secondary phenomenon accompanying or caused by not being depressed. To address this issue, McClintock performed confirmatory factor analysis, which measures religiosity in multiple variables, to respond to the critiques. They found that previous MDD diagnosis was associated with lower religiosity ($\beta = -0.15$, $p < 0.05$). Measures of religiosity were stable across depression histories of single individuals and familial risk groups, indicating religiosity is not an artifact of depression status.

The Enigma of Religious Belief

This paper discussed the multidimensional neuroprotective effect of a religious belief system, but the involvement of religion in the onset and recurrence of MDD is far more complicated. On one hand, statistical and psychological studies point out the association of religiosity with lower risk of MDD. For example, Miller utilized logistic regression analysis and concluded high importance of religiosity predicted as high as one-tenth of the risk of experiencing MDD in the ten years following assessments. Anderson derived a 75% protective effect against depression during middle adulthood for people with high personal importance of religion in early adulthood. On the other hand, such benefits do not always stand. Religious struggle, also known as negative religious coping, encompasses a troubled relationship with the deity and religious community and personal struggles in search of religious significance (Pargament). Research has demonstrated that religious struggle often leads to negative health outcomes and contributes to depression. In a systematic review of 195 scientific studies on religiosity/spirituality and MDD, Braam and Koenig concluded that religious struggle is significantly associated with more depression ($d = 0.30$) in 59% of the studies (22 included). Religious struggle negatively impacts functions of the HPA axis, with greater levels of struggle associated with higher cortisol levels throughout the day (Isehunwa). After controlling for baseline health and demographics, religious struggle increases death risk in elderly people with illnesses (Pargament). Many results are still controversial. Research suggested that high religiosity varies in protective efficiency for different age groups, although the pattern is yet not well-studied. Indeed, the neuroprotective role of a belief system involves a lot of nuanced discussions which I hope future scholars can further address.

In this essay, the word religiosity denotes both religious importance and personal spirituality for brevity. There is not a single defining feature which sets these two concepts apart, and they are often used interchangeably in a scientific context. For example, spiritual meditation usually refers to meditation in a religious context where people meditate to connect to the divine. However, demographic research in recent years indicates

a decline in people who say they are religious and an increase in the popularity of personal spirituality (Pew Research Center 2017). There might be an existing consensus on the differences between religiosity and spirituality. Clarification, or even separation, of these concepts in future neuroscience research will contribute to better understanding of this topic.

There is no definitive proof that the belief itself is the cause of the aforementioned benefits. I recommend future researchers specify the exact aspects of a belief system that grant the protective effects. This might allow for broader clinical applications, where areligious people with parental depression can follow certain procedures to acquire the same benefits as those with high religiosity.

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