RELIGION, BRAIN & BEHAVIOR, 2017
http://dx.doi.org/10.1080/2153599X.2016.1267035

Effect of a one-week spiritual retreat on dopamine and serotonin transporter binding: a preliminary study

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ABSTRACT

Spiritual retreats are a commonly used intensive program of meditation and prayer, along with other elements, designed to provide participants with opportunities for spiritual and psychological growth. While individual elements of such retreats have been studied, there have been no reports in the literature regarding the neurophysiological effects of these retreats. This preliminary study presents the first data we are aware of on the neurophysiological effects, particularly those related to dopamine and serotonin, in a group of participants undergoing an intensive seven-day spiritual retreat. We used DaTscan single photon emission computed tomography (SPECT) in 14 individuals before and closely following participation in a seven-day spiritual retreat. We observed significant decreases in dopamine transporter binding in the basal ganglia and significant decreases in serotonin transporter binding in the midbrain after the retreat program. Participating in the retreat also resulted in significant changes in a variety of psychological and spiritual measures. We also report the relationship between neurophysiological and subjective measures along with a discussion of potential methodological challenges for future studies.

ARTICLE HISTORY
Received 12 June 2016
Accepted 26 November 2016

KEYWORDS
dopamine; serotonin; SPECT; transporter; meditation; prayer; spirituality

Introduction

Spiritual retreats, immersive multiday practice environments, help people towards creating personal spiritual or psychological growth regardless of their religious beliefs. Retreat programs have developed out of a number of traditions, even secular ones, and have been increasing in popularity. For example, a *Time* magazine article reported that many Christian monasteries are now booked months in advance (Edwards, 2001). Likewise, Yoga and meditation retreats are a growing alternative to vacations due, in part, to perceptions regarding their therapeutic value (Hoyez, 2007; Smith & Kelly, 2006). Both secular and religious retreats are often associated with strong emotional responses, reduced stress, enhanced well-being, spiritual transformation experiences, and even result in life-changing consequences (Falkenström, 2010; Hood, 1977; Jacobs et al., 2013; Kennedy, Abbott, & Rosenberg, 2002). However, no studies have explored the neurophysiological effects of these retreat programs.

The Ignatian retreat is based on the Spiritual Exercises developed by St. Ignatius of Loyola (1491–1556), the founder of the Society of Jesus, known as the Jesuits. The Spiritual Exercises is a commonly used approach within the Jesuit community and by laypersons to bring about strong spiritual experiences. This retreat utilizes various elements including prayer, meditation, silence, and individual

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guidance throughout the retreat in order to facilitate spiritual experiences and even spiritual or personal transformation. These transforming experiences can have long-term consequences for the individual, which may be reflected in a number of psychological and physiological parameters. Because of its long history and high likelihood of strong experiences in a relatively short period of time, the Ignatian retreat is an ideal program to study the impact of spiritual retreats on a person's psyche and neurophysiology. However, to our knowledge, no longitudinal studies of the neurophysiological effects of such retreats have ever been reported.

On a more clinical level, practices associated with spiritual retreats, such as meditation, are among the most widely used alternative therapy techniques, with more than a third of respondents to national surveys on complementary and alternative medicine utilization indicating that they used meditation or prayer techniques (Wolsko, Eisenberg, Davis, & Phillips, 2004). Meditation techniques have also been used as an intervention in the treatment of various physical and psychological disorders. Initial reports suggest that meditative practices have effects in patients with hypertension, psoriasis, irritable bowel disease, anxiety, and depression (Astin, Shapiro, Eisenberg, & Forys, 2003; Bonadonna, 2003; Fjorback et al., 2013; Kabat-Zinn et al., 1992; Olex, Newberg, & Figueredo, 2013; Reibel, Greeson, Brainard, & Rosenzweig, 2001).

Although there is a growing research base on the physiological effects of meditation using functional brain imaging (Brefczynski-Lewis, Lutz, Schaefer, Levinson, & Davidson, 2007; Goldin & Gross, 2010; Lazar et al., 2000; Lutz, Brefczynski-Lewis, Johnstone, & Davidson, 2008), the biological mechanism of action of a more intensive spiritual retreat has yet to be well studied. There are several studies that have explored the longitudinal effects of meditation practices and retreats (MacCoon, MacLean, Davidson, Saron, & Lutz, 2014; Newberg et al., 2010b; Saggar et al., 2015), but most neuroimaging studies have focused on short-term changes during the practices themselves rather than long-term effects. The present study makes an important step towards understanding the neurophysiological effects of prolonged and intense spiritual exercises that are part of a seven-day Ignatian retreat (although the retreat is traditionally 30 days, it has been adapted to seven days by many retreat centers in order to make it easier logistically for people to participate). In this article, we present the first data from this study. We utilized single photon emission computed tomography (SPECT) imaging with I-123 ioflupane (DaTscan) to measure changes in both the dopamine transporter (DAT) and serotonin transporter (SERT) before and after subjects participated in the seven-day spiritual retreat. Given the psychological and spiritual changes anticipated, it was hypothesized that there would be significant changes in the dopamine and/or serotonin system.

Dopamine participates in the mediation of cognition, emotion, and movement (Cropley, Fujita, Innis, & Nathan, 2006; Remy & Samson, 2003; Stein, 2008; Takahashi, 2013), all of which are affected by spiritual retreats. Specifically, dopamine is involved in reward pathways by inducing positive emotions, motivation, and also improved cognitive abilities (Carlezon & Thomas, 2009; Delgado, 2007; Mozley, Gur, Mozley, & Gur, 2001). In addition, increased release of dopamine has been observed after meditation practice using positron emission tomography (Kjaer et al., 2002). The reason for using DaTscan is that the dopamine transporter is one of the primary regulators of dopaminergic tone. The reuptake of intact dopamine molecules from the synaptic cleft is performed by a macromolecular complex which is embedded in the axonal membrane (Giros & Caron, 1993) and allows excess, free dopamine to be physically moved, or "transported," across the axonal membrane against a concentration gradient. The rate at which dopamine is removed from the synaptic cleft may be the primary mechanism for maintaining dopaminergic tone. Thus, if there are changes in the dopamine system, perhaps in response to undergoing a spiritual retreat, then we would expect there to be a concomitant change in DAT binding.

Serotonin, or 5-hydroxytryptophan (5-HT), is a neurotransmitter found in the brain, spinal cord, and enteric nervous system. Serotonin transporters (5-HTT) are macromolecular complexes that are designed to remove serotonin from the synaptic cleft and move it intact back into the neuronal cytoplasm where it can be repackaged for re-use or metabolized. Serotonin transporter sites are located on 5-HT nerve terminals and on somatodendritic sites on 5-HT cell bodies. Since serotonin appears to be particularly involved in basic emotional responses and mood (Kranz, Kasper, & Lanzenberger, 2010; Stein & Vythilingum, 2009), if clinical changes occur as the result of a spiritual retreat, we would again expect there to be changes in the SERT binding.

DaTscan is a currently approved radiopharmaceutical with non-selective binding such that it enables measurement of both the DAT and SERT in a single scan. DaTscan binds to the DAT in the basal ganglia (where there is minimal SERT) and the SERT in the midbrain (where there is minimal DAT) so that we can measure both neurotransmitter systems with a single scan. DaTscan requires pre-administration of Lugol's solution, which helps to block the thyroid gland from exposure to the I-123 isotope that is part of DaTscan. This is standard protocol for diagnostic studies of this type. DaTscan is injected intravenously and then SPECT imaging is performed approximately three hours post injection. The images can then be quantitatively analyzed to determine SERT and DAT binding by analyzing the midbrain and basal ganglia regions respectively. SERT and DAT activity has been widely evaluated in a number of disease states such as Parkinson's disease and depression (Amsterdam, Newberg, Soeller, & Shults, 2012; Booth et al., 2015; Politis, 2014). DaTscan is therefore an excellent tracer for its cost, availability, and ability to quantify changes in SERT and DAT binding in association with a spiritual retreat.

Another important point regarding the DaTscan tracer is that it is not a state marker, but rather a trait marker. In other words, it does not change on a moment to moment basis but rather reflects tone of the dopamine system over a period of time (Mozley et al., 2001). The only way to directly affect the binding of DaTscan in the moment would be to administer a specific drug that blocks the dopamine transporter, such as cocaine or methylphenidate. Otherwise, the dopamine transporter requires time to change, which is why we thought this would be an excellent tracer to evaluate dopamine function associated with a week-long retreat. This tracer would not change over the course of a single meditation or prayer session, and would also not reflect effects occurring during the scanning day itself, but rather requires a period of time to change. Thus, if subjects are more comfortable undergoing the scanning the second time (i.e., the post-retreat scan) because of their familiarity with the imaging protocol, this would not be reflected in changes in DaTscan binding. In addition, there is extensive experience with related dopamine transporter tracers in our laboratory and others that show great stability of dopamine transporter binding over a period of weeks or months, indicating that simply repeating the scans does not result in substantial changes (i.e., less than 10% variability) in dopamine transporter binding (Booij et al., 1998; Mozley et al., 2000; Seibyl et al., 1997).

Therefore, the goal of this study was to determine whether the seven-day spiritual retreat resulted in changes in DAT and SERT binding using DaTscan SPECT and to correlate any imaging changes with qualitative changes in emotional or spiritual measures.

Methods

Subjects and imaging acquisition

The study protocol and consent form were approved by the Human Institutional Review Board at Thomas Jefferson University. Subjects were recruited from the local community by advertising with local pastoral care departments and churches. Subjects were permitted to report prior intense religious and spiritual experiences and also to have participated in prior spiritual retreats but could not have participated in the one-week Ignatian-based retreat. All subjects underwent an extensive medical and psychiatric history (First, Spitzer, Gibbon, & Williams, 1997) to ensure that none of the study subjects had a disorder that might affect cerebral physiology (i.e., stroke, tumor, epilepsy, active Axis I psychiatric disorders). All subjects had a single, initial evaluation with the DaTscan and a battery of psychological and spiritual questionnaires within one month of entering into the seven-day spiritual retreat. This represented their baseline or pre-retreat evaluation and was limited to a single time point primarily due to the expense of the DaTscan and also to minimize radiation exposure. They then participated in the retreat and returned as quickly as possible logistically after completing the retreat to repeat the scans and questionnaires (see Table 1 showing the time period for the pre- and post-retreat evaluations for each subject). All subjects returned within one week of completing the retreat for the post-retreat evaluation, but two subjects had to be scanned out of that range (12 and 14 days post retreat) due to logistical issues with scheduling the scans. No specific differences were observed in these scans compared to the others.

All subjects met the following inclusion criteria: (1) Able to give informed consent and willing to complete the study; (2) Willing to go through the seven-day spiritual retreat; (3) Willing to undergo the full imaging procedures; and (4) Women of childbearing potential having a negative serum pregnancy test. Subjects were excluded if: (1) They had any neurological or psychiatric disorders, including drug or alcohol abuse, that may interfere with cerebral physiology; (2) They had any medical conditions that may interfere with cerebral physiology; (3) They were currently taking medication that might affect cerebral physiology (i.e., antidepressants, antipsychotics, anxiolytics, benzodiazepines, sedatives, anti-seizure medications); (4) They were unable or unwilling to lie still in the scanner (i.e., due to claustrophobia or weight > 350 pounds); and (5) They had undergone previous brain surgery or had intracranial abnormalities that may complicate interpretation of the brain scans (e.g., stroke, tumor, vascular abnormality).

After inclusion and exclusion criteria were met, we recruited a total of 14 subjects to participate in the study. Subjects were eight males and six females. The subjects ranged in age from 24 to 76 with a mean age of 54 ± 13 years. All subjects were Christian in their faith origin, with seven Catholics, five Protestants, one Orthodox/Anglican, and one Quaker. Eight subjects reported experience with different types of religious or spiritual retreats, but no subjects had undergone this specific seven-day retreat.

Retreat description and components

The overall goal of the seven-day spiritual retreat used in the current study is to create an entirely new understanding of an individual's spiritual life and how this new understanding of spirituality can be incorporated into the person's everyday life as well as produce a substantial change and/or deepening of the person's spiritual and religious beliefs. All subjects underwent the retreat at the Jesuit Center at Wernersville in Wernersville, Pennsylvania. The retreat center itself is located in central Pennsylvania and is situated on 240 acres of a very natural and quiet site with beautiful grounds

Table 1. Change in specified regions for each subject between the pre- and post-retreat scan with the number of days before and after the retreat at which time the scans, and subjective data, were acquired.

Subject	Pre Scan[a]	Post Scan[a]	R Caud	L Caud	R Put	L Put	MB
001	6	2	−6.9	−2.5	−1.2	−8.8	−2.8
002	19	1	−17.0	−7.1	−9.0	−6.7	2.7
003	10	3	−18.6	−8.3	0.4	−3.2	3.2
004	10	3	−32.9	−18.3	−33.2	−27.4	−3.7
005	6	2	−3.9	−0.6	−0.8	−14.0	−26.6
006	30	7	−15.8	−6.8	−22.3	−16.2	24.1
007	25	2	−5.0	−6.6	1.4	5.4	−7.9
008	25	1	−1.0	0.0	−1.2	−2.3	−8.3
009	25	1	−19.5	−7.8	−21.5	−23.0	−13.4
010	12	2	−1.1	−11.9	−0.6	−8.6	−4.3
011	12	7	−4.3	−6.3	−17.5	−17.5	−16.9
012	20	5	−45.6	−43.8	−34.8	−38.4	−2.3
013	8	5	−20.4	−32.6	−38.3	−32.6	−17.9
014	20	5	−3.2	−4.7	−10.0	−3.4	−8.4

[a]Given as days before entering and after completing the retreat.
R Caud = Right caudate
L Caud = Left caudate
R Put = Right putamen
L Put = Left putamen
MB = Midbrain

and art. Retreatants can take advantage of the grounds and natural beauty as part of the retreat. The retreat is primarily performed in silence. On the first day, the individual meets with a spiritual director (usually a priest or nun) who provides daily guidance and insights regarding the direction of the retreat ("discerning the movement of the Spirit," according to the center's website). The retreat is based on the Ignatian exercises (Mottola, 1964), but does not follow them directly. The day consists of morning mass and extensive time spent in personal reflection, contemplation, and prayer. There is a daily meeting with the spiritual director. Meals are eaten in a common dining area with other retreatants, but typically maintain the overall silence of the retreat.

Psychological and spiritual measures

Before and after the retreat, subjects completed several psychological inventories and spiritual scales at the time of imaging. These well-established tests were validated originally in large populations of people, and have since been used in both clinical and research settings extensively. The battery of psycho-spiritual measures included the following tests: the Speilberger State Trait Anxiety Inventory (STAI-Y); the Profile of Moods Scale (POMS); the Beck Depression Inventory (BDI) (Beck & Beck, 1972); a 12-item Short Form Health Survey (SF-12); the Cloninger Self Transcendence Scale (Cloninger & Zohar, 2011); the Brief Multidimensional Measure of Religiousness/Spirituality (Fetzer Institute/National Institute on Aging Working Group, 1999); and the Index of Core Spiritual Experiences (INSPIRIT) (Hill & Hood, 1999).

DaTscan image acquisition, analysis, and statistics

All DaTscan SPECT studies were performed according to standard clinical protocol. Initially, subjects were given Lugol's solution 30–60 minutes prior to DaTscan injection. An intravenous catheter was placed in the arm and subjects were then injected with 3–5mCi of I-123 DaTscan. The intravenous catheter was removed and the tracer was allowed to circulate for three hours. Subjects were put in the scanner in the supine position with their head placed in a special head holder. All scans were performed on a Philips Forte (Philips, Andover MA) dual head SPECT scanner equipped with ultra-high-resolution collimators. Images were acquired over approximately 30 minutes and were reconstructed in the axial, sagittal, and coronal planes. Image reconstruction was performed on the Philips software associated with the scanner using filtered back projection with Chang's first order attenuation correction.

For analysis, the scans were reconstructed and resliced, using an oblique reformatting program, according to the anterior-posterior commissure line so that all scans were at comparable orientations for the analysis. We used the MIMneuro® software system for quantitative analysis of the DaTscan images, which also compares scans to a normative database of 32 subjects. All images are initially converted into a DICOM format for uploading into the MIMneuro program. The MIMneuro program then uses its Brainalign™ software to realign all scans into a standard anatomical space. The next step is that regions of interest (ROIs) are automatically placed on the primary structures of the basal ganglia, specifically the caudate and putamen, which are the primary areas to which DaTscan binds for the DAT (see representative Figure 1), and the midbrain, which is the primary area to which DaTscan binds for the SERT. The primary outcome measure is the Distribution Volume Ratio (DVR) in which the mean counts in the ROI is compared to a reference region (occipital lobe which has no significant DAT binding) at three to four hours post administration, when the distribution of DaTscan has approached a transient, near equilibrium-like state that reflects the k3/k4 ratio and is related to the binding potential (Acton et al., 1999). This allows for a quantitative assessment of DaTscan binding. The MIMneuro software also allows for a comparison to a normative database.

Using SPSS software for statistical analysis, the DVR for each ROI was compared between the pre- and post-retreat scan using a paired t-test analysis. Similarly, the pre- and post-retreat psychological

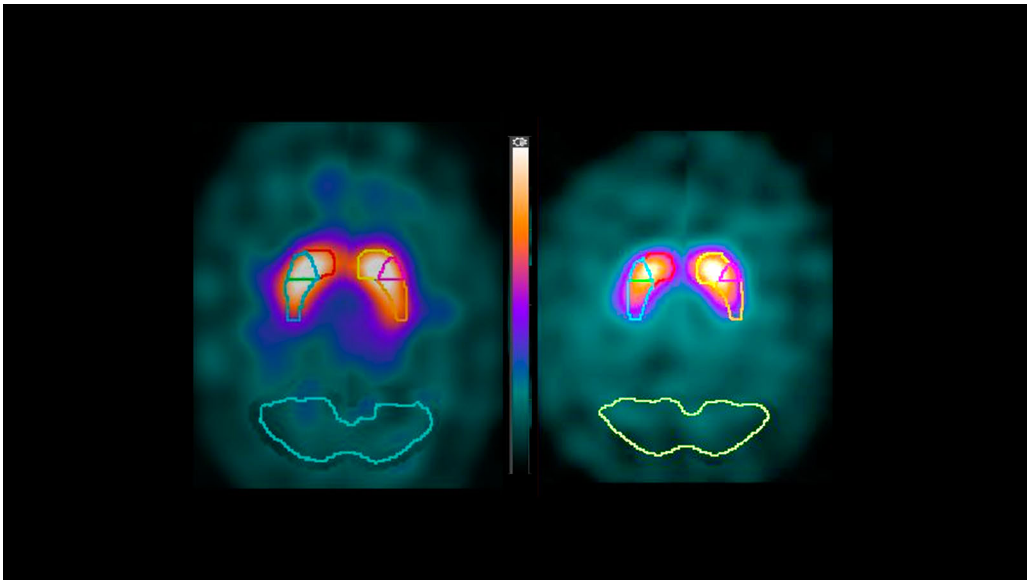

Figure 1. DaTscan images of a single retreat subject showing the regions of interest used for the analysis as well as the overall reduction in binding (reduced orange/red coloring when comparing the pre-retreat (left) and post retreat (right) scans.

and spiritual measures were also compared using paired t-test analysis. Using a linear regression model, we correlated changes in DAT and SERT binding with the qualitative measures found to show significant differences between the pre- and post-retreat questionnaires. We used the False Discovery Rate method to correct our data for multiple comparisons (Benjamini & Hochberg, 1995).

Results

The initial, pre-retreat scan results showed that the patients all fell within the normal range of DAT binding values compared to the normative database of 32 subjects provided as part of the MIM-neuro® software. The results for the DaTscan binding showed significant reductions in the post-retreat scans compared to the pre-retreat scans (see Table 1 for individual patient results and Table 2 for the overall results from the group analysis). All p-values survived correction for multiple comparisons using the False Discovery Rate method (Benjamini & Hochberg, 1995). The mean reductions, from 5–8%, were symmetric and were found in both the caudate and putamen regions (see Figure 1). Similarly, there was a significant reduction of 6.5% in the mean midbrain SERT binding on the post-retreat scans.

On the psycho-spiritual measures, there were several significant changes as a result of participating in the spiritual retreat. Based upon the SF-12, subjects subjectively perceived their physical health to be improved, with a physical component score of 52.2 ± 6.2 initially and 55.0 ± 3.2 post retreat

Table 2. Changes in DAT binding in the basal ganglia and SERT binding in the midbrain on the pre- and post-retreat scans. The p-value represents the significant difference between the pre- and post-retreat scans. All p-values survived correction for multiple comparisons using the False Discovery Rate method.

Brain Structure	*t*-statistic (df = 13)	*P*-value	Pre-retreat Mean ± SD	Post-retreat Mean ± SD
Right caudate	3.54	0.001	4.57 ± 0.66	3.92 ± 0.76
Left caudate	3.03	0.004	4.43 ± 0.63	3.91 ± 0.73
Right putamen	3.25	0.003	3.94 ± 0.62	3.40 ± 0.77
Left putamen	3.99	0.001	3.83 ± 0.67	3.27 ± 0.71
Midbrain	2.12	0.027	1.67 ± 0.21	1.56 ± 0.19

(t(13) = 1.87, $p = 0.04$). On the POMS, there were significant improvements (decreases) in the measure of tension (6.2 ± 6.1 pre retreat and 2.1 ± 2.2 post retreat, t(13) = 2.62, $p = 0.01$) and fatigue (4.4 ± 1.4 pre retreat and 2.7 ± 2.1 post retreat, t(13)] = 2.94, $p = 0.01$). There were no significant differences in depression or anxiety scores, in part because most subjects did not report high amounts of depression or anxiety at baseline.

Not surprisingly, on the Brief Multidimensional Measure of Religiousness/Spirituality, subjects reported more intense religious and spiritual beliefs (6.7 ± 1.2 initially and 7.4 ± 1.0 post retreat, t (13) = 1.88, $p = 0.04$). And subjects reported that they felt more religious (3.1 ± 0.8 initially and 3.5 ± 0.7 post retreat, t(13) = 2.69, $p = 0.01$) and more spiritual (3.6 ± 0.5 initially and 3.9 ± 0.4 post retreat, t(13) = 1.88, $p = 0.04$). On the Cloninger Self Transcendence Scale, there was a significant increase in feelings of self transcendence (18.2 ± 9.0 initially and 20.1 ± 6.0 post retreat, t(13) = 2.42, $p = 0.01$). There were no significant changes in the INSPIRIT scores.

We were also interested to see whether there were any relationships between the significant changes observed in the psychological and spiritual measures and the DaTscan findings. There was a significant correlation between the change in the Cloninger Self Transcendence and the change in DAT binding in the right caudate ($R = 0.66$, $p = 0.01$) and the right putamen ($R = 0.75$, $p = 0.002$). These survived a correction for multiple comparisons. In addition, there was a trend in the correlation between the change in the subjects' overall sense of religiosity and spirituality (added together) and binding in the right putamen ($R = 0.53$, $p < 0.05$), which did not survive correction for multiple comparisons.

Discussion

This is the first study we are aware of that has attempted to measure changes in the dopamine and serotonin systems as the result of participating in an intensive seven-day spiritual retreat program, in this case based upon the Ignatian exercises. The findings, although preliminary, suggest that participating in a spiritual retreat can have a short-term impact on the brain's dopamine and serotonin function, and that this might relate to various emotional and spiritual measures.

This study and its design, though, perhaps raises more questions than answers. For example, the spiritual retreat we studied has multiple elements including meditation, silence, prayer, self-reflection, and personal spiritual guidance (Mottola, 1964). Some of these practices, meditation in particular, have been studied more extensively in recent years and have been found to elicit a number of neurophysiological and subjective changes. Our prior research, as well as that of many others, has utilized functional magnetic resonance imaging (fMRI), PET, and SPECT to evaluate changes in cerebral blood flow during meditation and prayer states (Hölzel et al., 2011; Lazar et al., 2000; Lou et al., 1999; Newberg et al., 2001; Newberg, Pourdehnad, Alavi, & d'Aquili, 2003; Vago & Silbersweig, 2012). A number of changes have been reported that depend in large part on the type of meditation practice and the subsequent experiences (Newberg & Iversen, 2003). These functional neuroimaging studies of spiritual practices suggest that there is a network associated with such practices that includes changes in the attentional system of the brain including the prefrontal cortex, cingulate gyrus, and superior parietal lobes. There also appear to be changes of activity in the limbic areas such as the amygdala, hippocampus, and thalamus. However, these studies did not demonstrate changes over the course of the meditation and specifically did not evaluate changes over multiple time points. Several studies have also focused on the effects of performing a meditation practice over a period of time from days to years. Overall, there are both structural and functional changes associated with the long-term practice of meditation (Lazar et al., 2005; Luders, Toga, Lepore, & Gaser, 2009; Lutz, Greischar, Rawlings, Ricard, & Davidson, 2004; Newberg et al., 2010b; Pagnoni & Cekic, 2007). We are aware of only one PET study by Kjaer et al. (2002) that has explored the effect of meditation on dopamine or serotonin. That PET study showed an increased release of dopamine during the practice of Yoga Nidra meditation.

A major limitation is that there was no control group used. It is certainly very possible that other types of retreats, ranging from weekend retreats to seven-day retreats to longer ones, could all result in similar findings to those that we report here. It is known that various types of meditation programs, such as the mindfulness-based stress reduction program (Kabat-Zinn et al., 1992; Monti et al., 2012) and a prior Kirtan Kriya meditation study performed by our group (Newberg et al., 2010a), have resulted in neurophysiological and clinical changes. However, none of those studies evaluated the dopaminergic or serotonergic systems. Given the pilot nature of this study, we hope that future studies will be able to utilize one or more comparison groups including a "true control" group as well as active control groups in order to account for the many different variables and elements, including cohort effects and other sources of systematic variance.

The goal of the seven-day spiritual retreat used in the current study is to create an entirely new understanding of an individual's spiritual life and how spirituality can be incorporated into everyday life to produce a substantial change and/or deepening of spiritual or religious beliefs. For example, one subject reported the following:

> The seven-day retreat I participated in was singularly transformative and helped me connect more easily to Spirit and re-connect to God. Also, before the retreat, I would definitely say that I had a limited range of emotion, particularly not feeling very empathetic and not able to cry. But during the retreat, I felt the complete opposite and was much more in touch with a wide range of emotions.

Such a change might be reflected in other life domains, such as a person's psychological status, or perspectives on relationships and vocations. For example, one subject stated that "the retreat made me realize the need to re-prioritize aspects of my life, particularly putting God and Spirit before work."

We did find that there were significant changes in several psychological and spiritual measures. Most notably, there were significant increases in the subjects' reported level of spirituality and religiousness based on the Brief Multidimensional Measure of Religiousness/Spirituality, and in feelings of self transcendence. We also found that the change in religiousness and spirituality, along with feelings of self transcendence, correlated with the change in dopamine transporter binding, particularly on the right. It is unclear whether this laterality has an important physiological implication. Future studies with a larger sample size will be needed to elucidate the contribution of the hemispheres to religious and spiritual practices and experiences.

In the context of this study, we did not try to differentiate the effects of the various elements of the retreat, which include prayer, meditation, self- reflection, meeting with a spiritual director, silence, absence of external stimuli, and daily mass. In fact, by anecdotal report some subjects reported subjectively that they found the meditation or prayer component the most effective, while others felt the silence component of the retreat was most valuable. In addition, it is possible that other factors may have been the primary contributor to the findings, such as simply taking time off from work and daily stressors, being in a vacation-like environment, being in nature, meeting new people, or being in a new setting. Future studies will need to try to distill out these different elements to assess which ones are most effective and most related to the changes in brain function.

Another issue with our findings is that we might be evaluating the effect of emotional or spiritual experience itself rather than the effect of specific practices involved in the retreat. In other words, the practice of prayer might result in specific brain changes, but the subjective experience associated with that prayer (e.g., positive emotions, cognitive beliefs, spiritual feelings) might result in the brain changes. We might also be observing brain changes related to emotional status (i.e., reduced anxiety or depression) or other psychological and cognitive domains rather than anything spiritual.

We felt that it was important to establish whether any change occurred at all and then develop future studies to determine the most "active ingredients" of the retreat. In addition, future studies could evaluate other types of retreats, both spiritual and secular, to determine whether there are similar effects. Since there are so many different types of retreats, we were uncertain which type would constitute an appropriate comparison or control. One might wonder whether a Buddhist retreat, or simply going on a relaxing one-week vacation, would result in similar effects. In fact, research by several other groups, along with ours, has shown longitudinal changes in brain function associated with prolonged exposure to meditation retreats and practices (MacCoon et al., 2014; Newberg et al., 2010b; Saggar et al., 2015). Again though, we felt that we needed to first determine if any effects occurred before pursuing a larger-scale trial of multiple types of retreat programs.

Regarding our study design, the subject selection also raised important methodological challenges for this study and future studies. We enrolled subjects with reasonable experience of meditation or spiritual practices. However, it was unclear who would make the best subjects for this current study. On one hand, it might be argued that relatively novice individuals would be best since the intense spiritual component could have a larger impact on someone inexperienced in such practices. However, if a person has too little interaction with spiritual practices or retreats, he or she might be overwhelmed or confused by the retreat program and not be able to engage in it as fully as someone who was more familiar with it. Since our goal was to simply observe the effect of the retreat, we decided to not make the level of prior spiritual involvement a criterion for enrollment. Our only criterion was that the subjects were not permitted to have participated in this specific type of retreat before.

Another issue is that the retreat has a specifically Christian perspective, and hence we recruited only persons of Christian faiths. It should be noted that since these individuals were Christian, there may have been an inherent bias towards having a positive experience. Such social or spiritual desirability can have a substantial effect on subjective measures (Batson, Naifeh, & Pate, 1978). It is well known that biases of the subjects, especially when personally motivated, can affect the outcome of the studies (Adams et al., 2005; Paulhus et al., 1991; Phillips & Clancy, 1972). On the other hand, since the goal was to observe the impact of the retreat, it would make sense to include individuals who have a desire and goal of having a positive experience. In fact, several non-Christians expressed interest initially. However, when the content of the retreat was discussed, the potential subjects decided to decline. This raises important issues for future studies, in which it is important to enroll participants who are familiar and comfortable with the foundational belief system of the retreat program. But it is also important to try to develop study designs that can factor out subject beliefs and biases that might also contribute to the findings.

In terms of the emotional aspects of spiritual practices such as meditation and prayer, there are many that have been reported. As described in many religious and spiritual traditions, emotions associated with such practices include awe, love, compassion, joy, and ecstasy. For example, as measured by the Smith Relaxation States Inventory, Zen meditation has been found to be associated with higher levels of love and thankfulness (Gillani & Smith, 2001). Another study by Ritchie, Holmes, and Allen (2001) also found that diverse meditators report higher levels of prayerfulness, love, and thankfulness. Furthermore, specific studies have evaluated improvements in mood such as lower levels of depression and anxiety as the result of meditation practices (Kabat-Zinn et al., 1992; Miller, Fletcher, & Kabat-Zinn, 1995). A large study of a heterogeneous population of patients including those with cancer, HIV, musculoskeletal disorders, pain syndromes, anxiety, and depression showed a 34% reduction in the depression subscale of the Global Severity Index (Reibel et al., 2001).

It should also be noted that similar brain functions may be associated both with spiritual practices and with feelings of love. For example, the striatum, hypothalamus, cingulate gyrus, and parts of the frontal lobe have been shown to be involved when test subjects experience love or are exposed to pictures of loved ones (Bartels & Zeki, 2000; Fisher, Aron, & Brown, 2005; Kurup & Kurup, 2003). Other studies have also implicated the brain's dopamine mediated reward system as being associated with strong positive emotions such as love (Aron et al., 2005; Esch & Stefano, 2005). The previously described imaging studies of meditation techniques have also shown involvement of these same areas. Thus, it is reasonable to expect that there is a physiological relationship between feelings of love and compassion and spiritual practices. This concept is also supported phenomenologically since many describe increased feelings of love and compassion resulting from their spiritual practice.

Studies have also looked specifically at the dopamine and serotonin system in its relation to feelings of love and positive emotions (Kendrick, 2004; Marazziti, Akiskal, Rossi, & Cassano, 1999). Thus, dopamine plays a significant role in the reward system in the brain, resulting in positive emotions related to love, eating, and cravings (Fisher et al., 2005; Koob & Volkow, 2010; Kurup & Kurup, 2003). One interesting case report of an individual having an intensely positive emotional response during jhana meditation found increased activity in the nucleus accumbens involved with the striatum and dopamine circuits (Hagerty et al., 2013). These dopamine reward circuits may also play a role in both Pavlovian and instrumental conditioning (O'Doherty et al., 2004), which could also be related to the repetitive elements of religious practices or retreat programs. An fMRI study of repetitive prayer practices supports a relationship between dopamine and these practices. This study of 20 young Danish Protestant Christians showed activation of the caudate nucleus which is intimately involved with the dopamine reward pathways (Schjødt, Stødkilde-Jørgensen, Geertz, & Roepstorff, 2008). The authors suggested that results supported their hypothesis that, like other forms of repeated habits, praying would activate the human striatal dopaminergic reward system (Delgado, 2007).

Initial meditation studies have also suggested that the areas involved with serotonin are also affected by these practices (Newberg & Iversen, 2003). Interestingly, a case study of meditation with the use of sertraline (a serotonin reuptake inhibitor) showed that during a meditation retreat, the subject reported that "cognitive abilities and the emotions of fear and anger seemed unaffected. However, the emotions of sadness, happiness, rapture, and love were dramatically reduced in intensity and duration" (Walsh, Victor, & Bitner, 2006).

Thus, whether one evaluates the religious and spiritual literature or the scientific literature, there is substantial evidence of a relationship between positive emotions, including love and compassion, that are associated with spiritual practices such as those performed in the seven-day spiritual retreat in the current study.

Imaging the dopamine transporter in vivo has recently become the primary means of assessing the dopaminergic system in controls and patient populations, including those with movement disorders and depression. Our group has demonstrated changes in the DAT binding associated with Parkinson's disease and other movement disorders, as well as in depression and mania (Amsterdam et al., 2012; Weintraub et al., 2005). Dopamine transporter concentrations can now be visualized non-invasively with several radiopharmaceuticals, with DaTscan being the tracer currently commercially available. As mentioned above, dopamine participates in the mediation of cognition, emotion, and movement and helps regulate and coordinate the execution of many complex neuropsychological functions. The dopamine transporter is one of the primary regulators of dopaminergic tone.

Typically, DAT concentrations change slowly over time and thus are affected by the aging process as well as various interventions (Amsterdam et al., 2012; Mozley et al., 1999). Since we have previously observed no significant change over a period of several weeks to months in healthy individuals, we did not feel that an additional control group, such as a waitlist group, would be necessary. In addition, DAT binding on these scans has generally been reported to have good test-retest reliability (i.e., less than 10%), and has not been shown to be influenced by other factors such as medication use, circadian rhythms, climactic changes, or calendric effects. However, future studies will need to take into account other comparison groups such as different retreat types or those undergoing other types of interventions to determine whether the findings of the present study are specific to this spiritual retreat.

No study has determined whether a spiritual retreat consisting of the elements described in this study has an impact on the dopamine system that might be reflected in DAT binding. The finding of reduced binding within a healthy range after the retreat is an intriguing finding that warrants further study with larger sample sizes and better control of the different variables. Studies would first need to confirm whether such retreats truly result in a decrease in DAT binding since we had originally considered the possibility of either an increase or decrease in DAT binding associated with the retreat. An increase in DAT binding might have been explained as being related to a persistent increased release of dopamine associated with the positive emotions and practices such as meditation and prayer. If there was a persistent increase in dopamine release, the DAT would theoretically upregulate in order to accommodate the higher amounts of residual dopamine.

The reason and implications of the decrease in DAT binding we observed are unclear. If this reduction is related to the retreat, it would be helpful to compare the findings with specific elements of the retreat to determine if there are particular factors or experiences related to the decrease. Such correlations might help support this overall relationship. Although there were some correlations between DAT binding and feelings of self transcendence, and weakly with the sense of religiosity and spirituality, the current data are not strong enough, especially since other measures did not correlate significantly. Future studies with a larger number of test subjects could address whether the reduced DAT is simply related to emotional responses or may actually potentiate dopamine's effects as a kind of "priming" mechanism by which the brain becomes more sensitive to various internal or external stimuli. While this possibility is supported by a prior study from our group in which depressed patients had improved symptoms with decreased DAT binding after cognitive behavioral therapy (Amsterdam et al., 2012), it will be important to better evaluate what subjective effects associated with the retreat are actually related to changes in dopamine levels.

Serotonin, or 5-hydroxytryptophan (5-HT), is a neurotransmitter found in the brain, spinal cord, and enteric nervous system. Serotonin transporters (5-HTT) are macromolecular complexes that are designed to remove serotonin from the synaptic cleft and move it intact back into the neuronal cytoplasm where it can be repackaged for re-use or metabolized. Serotonin transporter sites are located on 5-HT nerve terminals and on somatodendritic sites on 5-HT cell bodies. They are widely distributed throughout the brain, but particularly dense on GABAergic and peptidergic neurons in the midbrain regions. We, and other groups, have found low SERT binding to be associated with depression (Kambeitz & Howes, 2015; Newberg, Amsterdam, Wintering, & Shults, 2012). However, we found significant decreases in SERT binding after the spiritual retreat even though the subjects reported improvements in mood and anxiety. Again, the meaning of the reduced serotonin transporter binding in this preliminary study is unclear. Future studies with larger samples and more comparison groups would be necessary to help confirm this finding and elucidate whether it is related to specific elements of the retreat itself or different subjective measures of emotions and spirituality for the individuals.

Overall, these preliminary data present some interesting information regarding the effect of intense spiritual retreats. There appears to be a decrease in DAT binding in the basal ganglia and SERT binding in the midbrain as a result of going through an intense one-week spiritual retreat. Whether this is related to the overall reduction in stress, specific elements of the retreat program, or some type of priming effect remains to be established. Perhaps most important given the preliminary nature of this study and the limitations of the study design mentioned above is that this study demonstrates that it is possible to measure dopamine and serotonin levels in association with spiritual retreats and practices. Thus, future studies can better utilize these neuroimaging techniques to better determine if intense programs such as the Ignatian spiritual retreat have a substantial short-term effect on the serotonin and dopamine neurotransmitter systems in the brain.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by the Fetzer Institute [grant number 2425.01].

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