RESEARCH ARTICLE

REVISED Healing through faith: meeting a chaplain coupled with biblical readings could produce lymphocyte changes that correlate with brain activity (HEALING study) [version 2; peer review: 1 not approved]

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v2 First published: 20 Dec 2021, 10:1295
<https://doi.org/10.12688/f1000research.74504.1>
 Second version: 24 Feb 2022, 10:1295
<https://doi.org/10.12688/f1000research.74504.2>
 Third version: 21 Mar 2022, 10:1295
<https://doi.org/10.12688/f1000research.74504.3>
 Latest published: 21 Jun 2022, 10:1295
<https://doi.org/10.12688/f1000research.74504.4>

Abstract

Introduction: Faith and systems of beliefs are known to impact not only the emotional, but also the immunological state of believers in ways that we are just starting to understand. Moreover, clinical implications of previous studies are limited.

The aim of the "HEALING" (Hospital-based Ecumenical and Linguistic Immuno-NeuroloGic) Study was to examine immunological and neurological changes in hospitalized patients after meeting a chaplain coupled with biblical readings.

Methods: Hospitalized patients were pre-screened to find those who were the most in need of an intervention. A passage from the Bible was read to them during a meeting with the chaplain at the bedside (n= 20) or in the chapel (n= 18). No meeting occurred in the randomized control group (n=19). Blood samples were taken 30

Open Peer Review

Approval Status

1

version 4

(revision)
21 Jun 2022

version 3

(revision)
21 Mar 2022

version 2

(revision)
24 Feb 2022

version 1

20 Dec 2021

minutes prior, and 60 minutes after the meeting to measure white blood cells (WBC), interferon gamma (IFN- γ), immunoglobulin M (IgM), IgA, IgG, and complement 3 (C3). A subgroup of the visited patients was subjected to functional magnetic resonance imaging (fMRI), where they were played an audiotape of readings of the same passage from the Bible (n=21).

Results: Lymphocyte counts increased more often after the more successful visits, but the immunological changes were not significant. Conversely, a significant ($p_{fwe}=0.003$) correlation was revealed between changes in lymphocytes and activation of the angular gyrus (left BA39) during fMRI, a brain area involved in word recognition.

Conclusions: Although limited by the sample size and cohort study design, the findings suggest the depth of psycho-immunological changes could depend on the degree to which the chaplains' main message is understood.

Keywords

faith, hospitalization, psychoneuroimmunology, theology, fMRI

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Any reports and responses or comments on the article can be found at the end of the article.

This article is included in the **Sociology of Health** gateway.

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Competing interests: Religious affiliations: Éva Perpékné Papp, Pál Bödecs, Judit Fodor and Tamás Németh are Reformed pastors, Ferenc Tomanek is Catholic priest. Private financing: Andrea Varga, MPharm is mother of Dr. Béres and sponsored the IFN- γ measurements. Private company affiliations: Antal Szilágyi, Marianna Kiss-Merki and György Nagyéri are employees at SoftFlow Ltd., the company that performed the IFN- γ measurements. The authors have no other competing interests to declare.

Grant information: The study was supported by the Foundation for the Kaposi Mór Hospital (PhD grant).
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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How to cite this article: Béres A, Emri M, Aranyi C *et al.* **Healing through faith: meeting a chaplain coupled with biblical readings could produce lymphocyte changes that correlate with brain activity (HEALING study) [version 2; peer review: 1 not approved]** F1000Research 2022, 10:1295 <https://doi.org/10.12688/f1000research.74504.2>

First published: 20 Dec 2021, 10:1295 <https://doi.org/10.12688/f1000research.74504.1>

REVISED Amendments from Version 1

A typo has been corrected in the legend of Figures 11 and 12.

More detailed revisions are to come once at least two reviewers have sent their reports.

Any further responses from the reviewers can be found at the end of the article

Abbreviations

BA: Brodmann area

fMRI: functional magnetic resonance imaging

NK cells: natural killer cells

NSAID: nonsteroidal anti-inflammatory drug

For other abbreviations, see [Table 1](#).

Introduction

After Selye's description on how stress modulates the immune system,¹ a wide series of studies have shown direct and complex relation between acute,²⁻⁵ chronic stress, and the immune system,⁶⁻⁹ with evidence revealing the long-term effects of early-life stress on the immune response.¹⁰⁻¹² Much less research has examined the modulating effect of positive emotions on immunity. Berk *et al.* found signs of immune stimulation among healthy adults after watching a humorous video.¹³ Later, Bennett *et al.* showed that the extent of immunological changes related to interventions intended to elicit positive emotions, may largely depend on the way these emotions are subjectively perceived: after showing a humorous videotape to healthy women, they did not find significant change in NK-cell activity as compared with the control group, only when they included the level of cheerfulness in their calculations; this was measured by counting the number of pre-established metacommunicative signals, from just smiling to laughing out loud, that indicate the amount of mirthful laughter elicited among the participants ("Humor Response Scale").¹⁴ Studies traced down how positive experiences can trigger immunological changes in a chain reaction all the way down to the genetic code – creating "molecular signatures" related to mind-body interventions.¹⁵

Most of the basic studies cited above were conducted with healthy adults, under non-clinical conditions, using non-personal tools (humorous videotapes), in the context of group sessions. The "SHoRT" study examined the immunological effect of positive emotions spurred by positive experiences of sick children being treated in a hospital.¹⁶ In the "HEALING" (Hospital-based Ecumenical and Linguistic Immuno-NeuroloGic) study presented below, the authors tried to elicit a positive emotional effect through a meeting with a chaplain in a pre-selected, adult population. Previous studies only examined the long-term effects of religious life on the immune system,¹⁷⁻¹⁹ or the relevant brain areas,²⁰⁻²² while neurological events have been studied in isolation from other physical changes; moreover, the concept of religious practice occurring in a hospital setting is a sensitive issue, posing many practical difficulties ("God at the bedside"²³). The "HEALING" study aimed to examine whether general psycho-neuro-immunological patterns could emerge from a single spiritual encounter within a clinical environment, or whether changes measured in previous studies were lost in the sea of other factors affecting the immune system.

Our trial is registered at www.ClinicalTrials.gov (Identifier: NCT04112121, Registration date: 02/10/2019).

Methods

Study design

The following randomized, parallel, open-labeled, controlled clinical trial study design was used:

1. Effect of biblical readings on immunological parameters

- Healing I. Measuring the effect of biblical readings at the bedside:** At the center of the measurement was the first meeting with the chaplain, coupled with biblical readings by the patient's bed. With this measurement, we tried to evaluate what immunological change the "acceptance of the Word" elicits. (In Christian religion, the listening of a passage from the Bible is considered to be a possible way of meeting God. Thus, in Christian terminology, the term "Word of God" refers either to a specific biblical passage, to the Bible in general or directly to the person of God²⁴). The first blood sample was taken 30 minutes prior, the second blood sample was drawn after listening to the reading, 120 minutes after the first sample. Twenty patients were evaluated for this portion of the study.

For the graphic overview of the study design presented above, see [Figure 1](#).

Measurements in the chapel (n = 18) occurred in five independent groups (minimum of three, maximum of five patients in each group). In three of the five groups (for 11 patients), we gave patients the option to receive communion: Catholic Eucharist, or Reformed Lord's Supper. Of the 11 patients, five opted to receive Catholic Eucharist (four patients) or the Reformed Lord's Supper (one patient).

The complete date range for participant recruitment was from 10 September 2015 to 2 January 2017; the nature of the interventions did not require follow up after 2 January 2017. There were no changes in trial outcome or methods after the trial commenced. The trial was stopped once the number of planned enrollments was met. We identified no harm or unintended effects on patients during or after the study.

For an overview of the enrollments, see HEALING study's CONSORT Flow Diagram (cf. Figure 1 in the *Extended data*).

The complete protocol was approved by the Hungarian Medical Research Council's Committee for Research Ethics (Appr.: 7245-1/2014/EKU (55./2014), authorization number: SOR/074/00130-4/2014), and our institutions' Internal Ethical Boards (IG/02013-003/2015; 270/2015). Written informed consent was obtained from all participants. The research was conducted according to the principles expressed in the Declaration of Helsinki.

Enrollment

Inclusion criteria were: adult age (>18 years), being hospitalized, the ability for verbal communication, alertness, orientation, no sign of psychosis in their medical history, and willingness to participate in the study after written, informed consent. The hospital's Infectious Diseases and Nephrology Wards were involved in the recruitment process. We proposed the enrollment for all patients satisfying the above criteria, except in case of any exclusion criteria. Mobility was also an inclusion criterium for the events taking place at the chapel and the fMRI measurements. Due to the chaplain's limited time availability, not all eligible patients were able to participate in the study. The decision was based on the patient's degree of need and willingness, as assessed by, and at the discretion of, the chaplain, using a quick stratification scoring system specifically designed to address the practical needs of this study (see Appendix 1, *Extended data*). Exclusion criteria were the inability to communicate verbally, psychotic state (as reported by the physician responsible for the patient), altered mental state, unwillingness to participate, active and treated malignant disease, steroid, oral non-steroidal anti-inflammatory drugs (NSAIDs) or metemazole- sodium use, since these could have influenced the measured immunological parameters.

Random assignment was based on the chaplain's availability on the day of the measurement, rather than chance allocation of all the patients willing to be visited, so that the results of the control group were not biased by disappointments or frustrations caused by the cancellation/postponement of an anticipated visit. Thus, the atmosphere in the control group reflected the genuine psychological environment of a common day at the hospital, undisturbed by out-of-the ordinary events. The randomized control group consisted of patients who knew the goal of the measurement but were explicitly asked to help with their participating in the control group, i.e., they knew they weren't going to meet the chaplain (by request, the encounter could be scheduled for a later occasion).

Enrollment was arranged by the investigator. In order to minimize allocation bias, a covariate-adaptive, blocked, stratified randomization method was used: block size was fixed to 19 (± 1) enrollments for each group, with a 1:1 allocation ratio. For the control group we enrolled patients whose diagnoses and number of days in the hospital was similar to the intervention groups, in order to ensure a good balance of participant characteristics, as the intervention groups were saturated.

Personal encounter with the chaplain with listening to the biblical passage, and psycho-immunological measurements

The same passage was read in both groups (Isaiah 40, 27-31 – see Figure 2). Among the five groups in the chapel, communion was offered to three groups: Eucharist for Catholics, and Lord's Supper for members of the Reformed church. We asked the patients and the chaplain to complete a questionnaire designed for the study (HEALING questionnaire, preliminary pilot testing, see Appendix 2, *Extended data*). In the groups at the chapel, we used the validated PSS-14 score.²⁵ We took blood samples 30 minutes prior to, and 60 minutes after the encounter; due to some anticipated differences in the length of the visits, which were about 30 minutes each, it was the time interval between the two samples that was fixed to 120 minutes. We supplemented the lab measurements with microscopic examination of the blood smears²⁶⁻²⁸ (see Figures 4, 5, and 6), and measurements of IFN γ - (Healing I), or immunoglobulin M-, A-, G-, and C3- levels (enzyme linked immunosorbent assays), as well as some blood clotting factors (partial thromboplastin time [PTT] and international normalized ratio [INR]) (Healing II).

For an overview of the measured psychological factors and immunological parameters, and the corresponding abbreviations, see Table 1.

In the case of nominal values, non-parametric, associative-tests (i.e., Kolmogorov-Smirnoff) were used; in the case of immunological parameters, a normality testing followed by a parametric, paired-samples t-test was used. For all parameters measured in the study, we performed a network-analysis using two different methods: a Bayesian analyzer developed at UTE Budapest,²⁹ and R package *IsingFit* [R code used: *IsingFit* (data, family = 'binomial', AND = TRUE, gamma = 0.1, plot = TRUE, progressbar = TRUE, lowerbound.lambda = NA, vsiz = 10)],³⁰ followed by a correlation analysis. The usually used p value of 0.05 was divided by the number of comparisons analyzed (Bonferroni correction).

„27 Why do you say, (...),
 And speak, (...):
 “My way is hidden from the LORD,
 And my just claim is passed over by my
 God”?
 28 Have you not known?
 Have you not heard?
 The everlasting God, the LORD,
 The Creator of the ends of the earth,
 Neither faints nor is weary.
 His understanding is unsearchable.
 29 He gives power to the weak,
 And to *those who have* no might He
 increases strength.
 30 Even the youths shall faint and be
 weary,
 And the young men shall utterly fall,
 31 But those who wait on the LORD
 Shall renew *their* strength;
 They shall mount up with wings like
 eagles,
 They shall run and not be weary,
 They shall walk and not faint.”

Figure 2. Read aloud to all patients in the bedside or chapel groups, and during subsequent fMRI-s. Isaiah 40:27-31. New King James Version (NKJV). Patients heard readings by the chaplain and in their native language, Hungarian, in the study.

Repeated biblical readings from audiotape and fMRI measurements

Later, an fMRI examination was carried out, which was contingent upon availability of the fMRI and the capability of the patients to be mobilized. After providing written informed consent, the patients enrolled in the fMRI examination were comforted to prevent any possible anxiety related to the measuring environment (narrowness and loudness often posing a challenge for patients), given instructions on the process, then laid down into the fMRI equipment, where they could hear the reading of the study on audiotape. Patients could stop the exam at any time by pressing a button.

To examine the regions of the brain that could be impacted by the current measurement, we performed fMRI measurements using a “block-design” technique in three functional states:

1. In the active (“a”) block, patients could listen to the same passage from the Bible that they heard from their hospital bed or in the hospital’s chapel. They could hear the biblical passage once again read by the chaplain, in their native language (Hungarian) and in modern translation (Figure 2).
2. In the control (“s”) block, the stimulus was a scientific text from audiotape, also read by the chaplain (Figure 3). Although this text was intelligible, it contained many difficult scientific words, and complex grammatical structures in Hungarian (a Finno-Ugric language), posing an intellectual challenge for patients.
3. For a reference state, we introduced a block exposed to silence (“c”).

The MRI examinations were performed using a 1.5T Siemens Magnetom Avanto MR scanner (Syngo software version VB17/A, Siemens Medical Solutions, Erlangen, Germany); for the timing of the stimulation and synchronization of data collection, Nordic Aktiva v1.1. equipment (Nordic Neurolab, Bergen, Norway) was used. For all patients enrolled, a structural 3D T1-weighted axial MP-RAGE recording (TE = 4.73 ms, TR = 1540 ms, TI = 800 ms, flip angle = 15°,

"A vital system of defense against the viruses are the interferons and the NK cells. The latter recognize and destroy the target cells (cancer cells, virus-infected cells) which do not, or do in a transformed state, have MHC I molecules on their surface. The NK cells are also able to bond IgG with their surface CD16 molecules (Fc receptors), and are therefore also able to bind antibodies to their surface. By the binding of antibodies, these innate (non specific) cells of defense can acquire an antigen-specific orientation, capable of cytotoxicity specified by (dependent on) the antibody (ADCC)."

Figure 3. Control text read to all patients in the bedside or chapel groups during fMRI-s. "Innate (non specific) immune system" (extract). From: Szalka A, Timár L. Infektológia [Infectology]. Budapest: Medicina; 2005. Patients heard the text read by the chaplain in their native language, Hungarian, in the study.

Figure 4. Activated lymphocytes – microscopic examination of blood smear in the Healing Study.

slice-thickness 0.8 mm, $0.9 \times 0.9 \times 0.9$ mm voxel-size) and a 3 sec. repetition time, 145 components' blood oxygenation level dependent (BOLD) recording sequence ($T2^*$ gradient echo, $TR = 3000$ ms, $TE = 42$ ms, flip angle = 90° , interleaved 4 mm axial slice thickness, 3.6×3.6 -pixel size) was performed. During the fMRI measurements, the stimulation always started with a 15-second-long block of silence, followed by seven sections of activation blocks for 60 seconds each. The latter constituted of a 30-second-long active, and a 30-second-long control section or silence. During the measurements, the "block design" type stimulation was performed in a "c $\rightarrow$ as $\rightarrow$ ac $\rightarrow$ as $\rightarrow$ ac $\rightarrow$ as $\rightarrow$ ac $\rightarrow$ as" sequence order for all patients.

Figure 5. Large granulated lymphocyte (LGL) - microscopic examination of blood smear in the Healing study.

Figure 6. Small condensed lymphocyte - microscopic examination of blood smear in the Healing study.

In the first phase of processing the fMRI image database, we assigned the T1-weighted structural images' transformation into the MNI152 atlas-space using the FSL 5.0 and ANTS 1.9 programs^{31,32}; using the segmentation algorithm of the FreeSurfer 5.0 software package³³ in native space, we created the so-called brain-T1 pictures, only containing the images originating from the surface of the brain. With the help of the brain-T1 pictures, we transformed the motion-corrected fMRI picture sequences into the T1-picture corresponding to the person in question, and then with the defined atlas-space transformation we transformed it into the MNI152 atlas-space.^{31,32} Finally, on all fMRI image sequences, after eliminating the first four recordings containing the T1-effect, we applied an 8 mm isotropic Gaussian filtering. We used the SPM12 software³⁴ to perform the statistical analysis on the created fMRI picture database at individual and population level. During the processing of the individual fMRI image sequences, using the a-c, a-s and s-c contrasts, we generated the statistical image databases (contrasting pictures) showing the differences between the effects of the various stimuli, which we used in the population-level analysis to statistically characterize the effect of the stimuli. Finally, we examined the

Table 1. Psychological factors and immune-hematological parameters assessed in the Healing Study.

Psychological factors	Immune-hematological parameters
<p>Based on the patient's answers to the HEALING "before" questionnaire:</p> <ul style="list-style-type: none"> • Patient's personal belief on how she/he got sick (BI1 and BI2) • Patient's desire for the visit (BII1, BII4) • Patient's satisfaction with her/his life (BI3, BI4, BI5, BI6) • Patient's self-assessed burden caused by the hospitalization (BI7, BIV) • Patient's personal belief on the way she/he will be healing (BII2, BII3) • Patient's personal faith (BII1) • Patient's religious practice (BIII2) <p>Perceived stress scale 14 items (PSS-14)</p> <p>Based on the patient's or the chaplain's answers to the HEALING "after" questionnaire:</p> <ul style="list-style-type: none"> • Patient's/Chaplain's overall satisfaction with the visit (AI and PI respectively) • Patient's assessment on the intimacy of the encounter (AII) • Chaplain's assessment on the patient's openness (PII) • Patient's assessment on the sincerity of the encounter (AIII) • Chaplain's assessment on the extent she could connect to the patient (PIII) • Patient's assessment on the trustworthiness of the chaplain (AIV) • Patient's/Chaplain's assessment on the emotionally turbulent, roiling effect of the encounter (AV, PIV) • Patient's/Chaplain's assessment on the emotional depth of the encounter (AVI, PV) <p>(abbreviations refer to the question number in the corresponding Healing questionnaire)</p>	<ul style="list-style-type: none"> • White blood cell count (WBC) • Neutrophils: change in <ul style="list-style-type: none"> ✓ neutrophil count (dNeut) ✓ percentage of neutrophils (dNeut%) • Eosinophils: change in <ul style="list-style-type: none"> ✓ eosinophil count (dEo) ✓ percentage of eosinophils (dEo%) • Basophils: change in <ul style="list-style-type: none"> ✓ basophil count (dBas) ✓ percentage of basophils (dBas%) • Monocytes: change in <ul style="list-style-type: none"> ✓ monocyte count (dMono) ✓ percentage of monocytes (dMono%) • Lymphocytes: change in <ul style="list-style-type: none"> ✓ lymphocyte count (dLy-abs) ✓ percentage of lymphocytes (dLy%) ✓ percentage of large granulated lymphocytes (dLGL%) ✓ percentage of small condensed lymphocytes (dSmallLy%) ✓ percentage of activated lymphocytes (dMiddleLy%) • Lymphocyte/neutrophil ratio –change in: (dLy/Neut) • Platelet count (Plt) • Interferon-gamma level (IFNγ) • Immunoglobulin M level (IgM) • Immunoglobulin A level (IgA) • Immunoglobulin G level (IgG) • Complement C3 level (C3) • Partial thromboplastin time (PTT) • International normalized ratio (INR)

differences in BOLD-answers linked to the active and control audio-stimuli, and their correlation with concrete clinical data corresponding to each patient. In the SPM analysis, in the comparison of the statistical differences between a-c, c-a, a-s, s-a, c-s and s-c activities, we sorted out the activation clusters containing a minimum of 100 voxels, with a Student-t = 3,58 threshold corresponding to the non-corrected $p < 0.001$ value from the SPM {T} pictures. We then used the MNI152 spatial coordinates of the cluster maximum, the maximal t-value, the corresponding FWE-corrected probability (peak-level inference), the size of the cluster and the FWE-corrected probability of the occurrence of the cluster (cluster-level inference) to characterize them.³⁴

Results

The enrollment period lasted one and a half years. We analyzed 57 patients in total. The median age of the patients was 64 (Healing I), 65 (Healing II), and 66 years old (control). The only criteria when enrolling patients for the control group was that the patient's age, type of disease, and days of treatment did not show considerable difference compared with the intervention groups; due to the small number of patients willing to participate, statistical stratification needed to be used with constraints (cf. Table 1, *Extended data*).

Part 1: Psycho-immunological changes measured after the experience of the meeting

To the question of whether they believe in God, the majority of patients (Healing I: 65%, Healing II: 77.8%) answered positively. Only 25%-38.9% of the patients responded that they actively practiced their faith. A total of 35% and 44.4% of the patients reported cathartic, or a very positive experience at the end of the measurement (maximal rating of 5/5 at Question "AI" in the HEALING "after" questionnaire, i.e., the patient's overall satisfaction with the visit, as reported on a single item rating scale). 60% and 66.7% reported the visits to be deeply emotional (rating of minimum 4/5 at Question "AVI" in the HEALING "after" questionnaire, i.e., the patient's assessment on the emotional depth of the encounter, as reported on a single item rating scale).

Figure 7. Changes in lymphocyte counts in Healing I (bedside) and Healing II (chapel) study. Columns show the number of patients. 1: lymphocyte count (Ly-abs) and percentage (Ly %) decreased; 2: Ly-abs and Ly % did not change in the same direction; 3: Ly-abs and Ly % increased.

Figure 8. Columns show the number of patients with lymphocyte count decrease, no change and increase, respectively; in case a meeting took place, numbers above the columns indicate the average of subjective scores (from 1 to 5) by which the artists (SHoRT) or the chaplain (HEALING) evaluated the encounter.

Although changes in immunological parameters appeared to show tendentious deviations in both groups (bedside and chapel, see Figures 7 and 8), after Bonferroni correction, these changes were not statistically significant. Similarly, we did not find significant changes in immunological changes in the control group, therefore we reported no considerable difference between the intervention and control groups either (changes in IFN γ -levels were not considered to be clinically relevant, because the variance of the values at baseline was too elevated between the control and the intervention groups; we reported a miscalculation error retrospectively identified among PSS-14 scores – they were subsequently corrected in the raw data) (see Tables 2, 3, and 4, *Extended data*). With the statistical tools we used, we did not find significant correlation between the immunological and the psychological parameters (see Figures 9-10). It is an interesting observation that for the patients who were willing to take part of the communion offered, we measured decrease in lymphocyte counts without exception (see Figure 7).

Part 2: Results of the fMRI measurement

We obtained evaluable functional Magnetic Resonance Images (fMRIs) from a total of 21 patients in the second part of the study.

Figure 9. Matrix showing all possible correlations measured between psychological factors and immunological parameters, with darker colors corresponding to stronger correlations. (A) Correlation analyses – Healing I; (B) Correlation analyses – Healing II.

The comparison of the “biblical reading” block with the “silence” block showed significant ($p < 0.001$) activation in the right- and left BA 22 (Wernicke) and right- and left BA41 (Primary Auditory) areas solely. The comparison of the “control” block with the “silence” block showed significant ($p < 0.001$) activation in the same areas solely.

After that, we performed several subgroup analyses to explore the correlations between the psychological factors or the immunological parameters, and the changes in fMRI activities between the “active” and the “control” blocks. We created the subgroups of patients according to the extent of the change that was measured in the psychological factors (chaplain’s overall satisfaction with the visit – “PI” – and patient’s overall satisfaction with the visit and on the emotional depth of the encounter – “AI”, “AVI” - as reported on the single item rating scales corresponding to the questions of the HEALING

Figure 9. (continued)

“after” questionnaire), or the immunological parameters (changes in the lymphocyte count [dLy-abs], percentage of lymphocytes [dLy%], and lymphocyte/neutrophil ratio [dLy/Neut], values as measured automated laboratory, changes in the percentage of large granulated lymphocytes [dLGL%] as measured with microscopic examination of blood smears). The subgroups contained approximatively similar (half-half) number of patients.

It was solely among the dLy-abs subgroups that there showed to be a tendency in regards to the change in fMRI activity. We found a weak difference between activity in the area of leftBA39 between the subgroup of patients who showed an increase in lymphocyte counts, versus the subgroup of patients who showed no relevant increase in lymphocyte counts ($p = 0.393$). No other psychologic or immunologic pair of subgroups showed any difference in regards of their change in fMRI activity.

After that, we aimed to correlate the dLy parameters with the areas showing change in the fMRI activity. An invert linear correlation emerged ($p = 0.019$ with dLy%, $p = 0.003$ with dLy-abs) between the change in activity of the left BA39 area and the change in lymphocyte counts (see [Figures 11-12](#)). Finally, we performed the correlation analysis between the change in fMRI activity between the “active”- “control” periods, and the dNeut, dLy/Neut, AI, AVI, and PI factors or parameters, but we found no significant correlation.

Accounting for both the correlation analyses and the subgroup analyses, altogether we examined only 12 factors or parameters, and therefore the level of significance was $0.05/12 = 0.00417$. The correlation between the left BA39 area and change in lymphocyte count remained significant after the Bonferroni correction.

study was to know whether patterns marked enough to overwrite the heterogeneity of diagnoses could be elicited by the meetings. The diversity of the patients' psychological and somatic conditions was managed by the encounter-centered study design, and the time interval between both data collections was relatively small (two hours), as compared to the length of the patient's stay in the hospital (ranging from several days, up to weeks). The difference between the control and the intervention groups did not affect the main, significant result found with fMRI examinations, since that part of the study was performed within an auto-control setting.

Although the measured immune changes were too small to be clearly distinguishable from other clinical effects, it is noteworthy that the results from the hospital bed show a striking similarity with those of the “SHoRT study”, where the children from whom blood samples were drawn in a non-painful way through branules, were visited by Smiling Hospital artists [SHoRT¹⁶]. It was once again the more successful visits that generated more marked changes in lymphocyte counts. However, the growing inconsistency in lymphocyte changes as patients got closer to the chapel, and especially the results of the group receiving communion, could refer to the sense of fascination and admiration mixed with tones of fear, as reflected by the psychological or religious term *tremendum* (see Rudolf Otto’s terminology of the “numinous” and “mysterium tremendum et fascinans” to describe the experience of the holy³⁶). While the primary purpose of the intervention was to elicit positive emotions, the authors found that the same biblical reading could cause a wide range of thoughts and feelings, and different facets of the same emotional pattern could be amplified: this included fear of God, a

Figure 11. dLy-abs vs. a-s fMRI at leftBA39. Change in lymphocyte count ("dLy") versus difference between activation during the active "a" and the control "s" block ("response") during fMRI at the leftBA39.

recurrent motive of biblical encounters between God and man. For instance, in the Book of Exodus, God says to Moses: "I will make all my goodness pass before thee ... Thou canst not see my face: for there shall no man see me, and live." (Exodus 33, 19-20, KJV). More measurements are needed to clarify the statistical significance of these observations.

Neurological viewpoint

First and foremost, it is worth noting that the most easily implementable technically, entailing the least possibility of error in the laboratory measurement, and automated lymphocyte count showed significant correlation with the fMRI results. This part of the study was not affected by the any unintended bias in the randomization process, since the fMRI part of the study was performed within an auto-control setting, for visited patients only. Yet, as Lieberman and Cunningham pointed out, whenever fMRI is used as a principal tool in a research setting, the number of measurements performed during each examination are so high that from a statistical point of view, even the use of the most conservative p values cannot rule out the possibility of type I errors, rendering the results of every fMRI study only meaningful following comparison with previous, and verification by subsequent studies, in case these also support the interpretations proposed.³⁷ The current paper discusses a plausible interpretation of the findings while further research is needed to confirm the results.

Given that we could not rule out potential effects of magnetic resonance on immunological parameters from the fMRI examination, we intentionally separated fMRI measurements from immunological measurements. We laid out the "block-design" setting we used based on a meta-analysis of 48 studies,³⁸ and works by Leff *et al.*,³⁹ and Beaucousin

Figure 12. dLy vs. fMRI at leftBA39. Change in lymphocyte count ("dLy") versus difference between activation during the active "a" and the control "s" block ("response") during fMRI at the leftBA39.

et al.,⁴⁰ who described different activation patterns on the fMRI of patients exposed to readings featuring different emotional content.

The fact that the comparison of the a-c and s-c periods resulted in a significant change in fMRI activity, whereas no difference was detected when comparing a and s, proves that the measurement was physiologically trustworthy: the patients heard the biblical readings, and control text likewise.

The biblical passage is an ancient, more than two and a half thousand years' old text with plain words, and simple language structure, and is thought to have originally been intended to offer comfort. In contrast, the control text contained many difficult words for the layman, had long and difficult to follow sentences, and contained several words with potentially fear-inducing connotations. Thus, the result of the correlation analysis suggests the change in lymphocyte counts is related to the subjectively perceived content of the biblical reading as opposed to control text by the patients. The fact that the changes in lymphocyte counts were not significant, despite some widening in the confidence intervals, signaled that these changes were subject to limitations by the circumstances and by the disease; however, the correlation of these changes with the fMRI-s indicated that even when biblical readings did not appear to have a physiological effect, they could have an ordering, arranging effect, along some specific guiding principle, on a key parameter like the lymphocyte counts.

According to neurosynth.org, previous scientific publications related to the region in the 2 mm area of the -52, -56, 26 cluster, have linked this area to the tactile and manual reconstruction of shape recognition, the learning of words, emotional speech, and the encoding of belief systems in neural pathways, and their linking with ethical decision making.⁴¹⁻⁴⁷ It must be highlighted that the only brain area that showed a correlation with any of the immune parameters measured in this study - the left BA39, gyrus angularis - was contralaterally the same that is activated during meditation on/recitation of Buddhist scriptures.²⁰ Although the depth of understanding could only mean cognitive understanding, due to the core nature of the phenomenon observed and the study design, it can also refer to broader spiritual experiences – which, in turn, can only partially be influenced consciously. Thus, the brain area involved in the correlation described above (gyrus angularis) could also be linked to the "Aha! moment", which contains cognitive and emotional components alike but is not, or only partially, subject to conscious influence.

Excursus: theological perspectives

The authors would like to warn against interpreting the results of the study solely in terms of healing being accelerated by intimate religious experience. The spiritual, religious nature of the phenomenon observed obliges the integration of the theological viewpoint in the careful interpretation of the results. For centuries in the European tradition, theology – originally in close association with other areas of the basic scholar fields "*septem artes liberales*" (seven liberal arts) - has been the delegated branch of academic studies as far as any aspect of the Bible was involved. More recently, modern research methodology has been embraced, especially by the reformed theologians of 20-21st centuries' academic Christian theology, rendering it a branch of science only differing from other specialties by the principal focus of its observations being the "Word of God" instead of the natural world.²⁴ This legitimizes the examination of how findings

relate to the relevant theological literature in the discourse of a study involving religion, especially in the case of a study which used a biblical passage at its core.

When one is examining the effect of the Word of God on man, trying to correlate it with any human parameter, dialectical theologians immediately emphasize the inherent asymmetry in the relationship between God and man. As Tillich submitted, we cannot control God with our will: “The experience of Spiritual presence does something that the human soul in itself cannot”⁴⁸ Thus, the theologian points out that the immunological and neurological changes described in the measurement did not happened to the patient’s efforts, but without their knowing it. The content itself of the biblical message does not hold the promise of immediate physical healing. According to the Bible, Jesus’ healings give the impression that those had a signal value. Jesus did not heal everybody (cf. the account of the healing at Lake Bethesda, Jn 5, 1-9), and in a critical moment he himself accepted his own death. There are instances when Jesus’ Gospel has been theorized to give strength not just to overcome the disease, but to endure it. Nevertheless, correlation also exists in theology. Tillich wrote: “The answers emerging from the event of revelation are comprehensible only if they are in correlation with the questions of our whole existence, the existential question.”⁴⁸ Tillich used the method of correlation mainly in respect of the dialogue between the Christian message and the contemporary society (culture). The present paper describes how the method of correlation can also be used in the dialogue between natural sciences, social sciences and theology. Indeed, in Christian religion, the encounter between God and man can take place within a human relation, or also during a biblical reading, i.e., listening to the “Word of God”.²⁴ In this context, the meeting with the chaplain could trigger the recollection of some genuine, primordial experience of meeting with the transcendent, a phenomenon that could be the expression of ancient, maybe even pre-Christian patterns buried in our collective subconscious, and bringing up ancient, genuine, instinctive reactions, according to Jung’s concept on the working mechanism of “archetypes”, i.e., of inherited inner patterns buried in the collective subconscious.⁴⁹ The simultaneous change of the nervous and immune systems that was recorded in the present study during repeatedly listening to the Bible, confirms the possibility that in addition of the psychological effects, general biological patterns could also be activated during the meeting of God and man. In line with this concept, beyond the personal healing stories, the Bible’s synoptic contain numerous accounts of mass healings – i.e., Mt 4,24.8,16.12,15.14,14.15,30.19.2.21,14; Mk 6,56; Lk 4,40.9,11 – giving the impression that the meeting with Jesus also brought about general healing effects in people.

The contradiction presented above – namely, that the Word of God would be healing, whilst the main message of the Word sometimes does not bear healing, but cross – is solved if we put the question and the results of our study in the context of modern theologians’ evolutionary theory, which states that religiousness and life of faith also have developmental aspects, therefore can be understood as having an evolutionary dimension, with a direction of growth, at times including the notion of suffering through the process (see Whitehead⁵⁰ and “process theology”), and thus cannot be considered as opposed to the natural sciences’ concept of evolution.

According to Pannenberg, “at the end of the 19th century in the first half of the 20th, sadly, Christian churches and theologians could not recognize that the teaching of evolution gives an unprecedented possibility for theology in regards of the possibility of its relationship with modern science. The fight against Darwinism was one of the mistakes resulting in the most serious consequences during the history of the relation of theology with sciences.”⁵¹ The findings of the current study can be a small contribution to support this position, and put a novel lighting on the fact that, despite the lack of significant and noticeable biological effects, some form of religious belief could so indefatigably spread over and survive in the whole human species up until that day. If indeed, depending on the depth of spiritual understanding, the religious experience could influence the lymphocyte count, then it could contribute to prevent or recover from the diseases, hence provide an evolutionary advantage in the sense the natural sciences use this term. On the other hand, from the theologian’s perspective, the goal of evolution is not the survival and accommodation in the narrow sense of the word. Teilhard de Chardin wrote: “as early as in St. Paul and St. John we read that to create, to fulfill and to purify the world is, for God, to unify it by uniting it organically with himself”, and God is “from this point of vantage in the heart of matter, assuming the control and leadership of what we now call evolution.”⁵² He states that “through human socialization, whose specific effect is to involute upon itself the whole bundle of reflexive scales and fibers of the earth, it is the very axis of the cosmic vortex of interiorization which is pursuing its course.”⁵² Pannenberg often alluded to Gods’ appearance in world history, in the person of Jesus, as an event that can be considered the portent, the anticipation of the future.⁵³ In this sense, healings are of signal value because they hint a precursory picture of a harmonious God-man relationship, including all its psychical and physical aspects – as Pannenberg wrote: if, “(like Teilhard de Chardin), we can consider life’s evolution as the process of the creation of life forms of increasing complexity and at the same time becoming increasingly introspective, then we can also state, that in the succession of different forms of life by the creatures, is expressed the increase in the shareholding of the divine Spirit, of life’s Spirit.”^{51,52}

Faith is an evolutionary advantage, in the theological sense because the goal of evolution is the increase in the shareholding of the divine Spirit.⁵² This is the end towards which the result of our measurement converges.

Data availability

Underlying data

Figshare: Healing Study Beres et al. - Part 1: Psychological and Immunological Changes after meeting a Chaplain coupled with Biblical Readings among Hospitalized Patients, <https://doi.org/10.6084/m9.figshare.16750384.v1>⁵⁴

Figshare: Healing Study Beres et al. - Part 2: fMRI Changes after meeting a Chaplain coupled with Biblical Readings and Recalling the Visits with Audiotapes among Hospitalized Patients, <https://doi.org/10.6084/m9.figshare.16751851.v1>⁵⁵

Extended data

Figshare: HEALING Study Beres et al. - F1000Research - extended data, <https://doi.org/10.6084/m9.figshare.17029715.v1>⁵⁶

Reporting guidelines

Figshare: CONSORT checklist for “Healing through faith: meeting a chaplain coupled with biblical readings could produce lymphocyte changes that correlate with brain activity (HEALING study)”, <https://doi.org/10.6084/m9.figshare.17029715.v1>⁵⁶

Data are available under the terms of the “figshare” repository (licence CC BY 4.0).

Data generated from the above raw data are included in this article.

Acknowledgements

We thank all patients who participated in this study for their engagement.

We thank András Falus MD, PhD, DSc, for his inestimable help in making this study possible.

We thank Péter Antal, PhD and Bence Bruncsics for their invaluable help in the statistical analysis of Part 1 (Psycho-immunological changes measured after the experience of the meeting) of this study.

We thank Tamás Szelestei, MD, PhD, and Josef Fuisz, ThD, their suggestions were instrumental for the final version of this article.

For English consultation, we would like to express our profound gratitude to Tricia Garrison, creative collaborator on the “Happiness Helps Healing” initiative.

We thank Andrea Varga, MPharm, mother of Dr. Béres, for having taken the risk to substantially sponsor the study.

With this study, the Kaposi Mór Teaching Hospital pays tribute to the 500th anniversary of the Reformation.

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Open Peer Review

Current Peer Review Status:

Version 1

Reviewer Report 21 February 2022

<https://doi.org/10.5256/f1000research.78267.r120035>

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Regarding the article entitled, "Healing through faith: meeting a chaplain coupled with biblical readings could produce lymphocyte changes that correlate with brain activity (HEALING study)", overall, this study is potentially quite interesting and would be of interest. However, the lack of positive results and the confusing presentation with heavy reliance on religious and theological discussion substantially limits the value of this article from a scientific perspective.

Introduction

The introduction needs to clearly state what the authors' hypotheses were. Without this, it is difficult to understand what they are trying to accomplish in their study. Do they think that lymphocyte counts will increase or decrease? What correlations are they expecting? What parts of the brain are they anticipating will be involved. They should consider elaborating on studies of mindfulness and other meditation practices on immune function.

Methods

The authors should clarify how subjects were allocated since they were not truly randomized, but allocated by convenience.

The authors state: The decision was based on the patient's degree of need and willingness, as assessed by, and at the discretion of, the chaplain...

What does this sentence mean? Is the chaplain deciding who is included in the study? This seems highly problematic.

The authors state: The randomized control group consisted of patients who knew the goal of the measurement but were explicitly asked to help with their participating in the control group, i.e., they knew they weren't going to meet the chaplain (by request, the encounter could be scheduled for a later occasion). Does this mean that they knew they were controls or just that they weren't meeting with the chaplain?

The authors state blood collections occurred 30 minutes prior to and 60 minutes after the spiritual intervention. Can they provide an explanation as to why this particular timing? Is this based upon any data regarding the speed with which these serum markers can change?

Regarding the passages read to the subjects, is it possible that the Isaiah chapter is something that the participants know well? Would it have been better to have read from some other passage of the bible such as a listing of names which has a potential neutral effect rather than something that is medically oriented?

Part I Results

This comes across as a very confusing section. The tables and figures are very confusing and in the end, it seems that no results were significant. Perhaps this section can be substantially altered to state that there were no significant findings. If there was a trend towards significance in any of the values, perhaps the authors can use this information to provide an effect size that might be useful for developing future studies. But otherwise, it does not seem appropriate to include tables and complex figures on data that is non-significant.

Part II Results:

Perhaps this was not clear, but were there differences between the active prayer block and the control block or just between prayer and silence? This might be particularly relevant and interesting in that hearing a religious recitation affects the brain differently than a neutral/scientific recitation. This might also be more relevant in terms of other physiological and psychospiritual measures. Otherwise, as with the section above, the authors should really only show the significant results and can delete Figure 11.

In the text, the authors state: *After that, we aimed to correlate the dLy parameters with the areas showing change in the fMRI activity. An invert linear correlation emerged ($p = 0.019$ with dLy%, $p = 0.003$ with dLy-abs) between the change in activity of the left BA39 area and the change in lymphocyte counts*

Can they clarify that this refers to the active minus silence condition? Again though, perhaps it would be more interesting to see correlations between the active and scientific control?

Discussion:

The first few sentences of the Discussion do not seem to be relevant to the main discussion and should be deleted:

Taking Salopek's "slow journalism" concept as a model [he makes a 21,000 mile-long journey (33,780 km) by foot, to retrace the pathways of our ancestors, the first humans who migrated from Africa and journeyed around the Earth - he posits that one must devote time to inter-personal connections in order to fully comprehend the human phenomenon - "Out of Eden Walk,"³⁵], we consciously stood for the concept of "slow science" for a slow pace of methodology.

In the Discussion, the authors refer to the auto-control setting. Can the authors clarify what they mean by this?

It is not clear why the SHoRT trial is being used for comparison since this was a study of children. It seems that the design is completely different as well focusing on artistic components rather than spiritual. This should either be deleted or expanded more to clarify why this is an appropriate study for comparison.

The authors state that the intervention was designed to elicit positive emotions, but may have resulted in other emotions as well. The authors should review articles on positive emotions and immune function. In addition, there should be greater clarification of what other emotions were elicited. Did they acquire data for this?

Can the authors clarify the following passage? What do they mean by a “guiding principle”? *however, the correlation of these changes with the fMRI-s indicated that even when biblical readings did not appear to have a physiological effect, they could have an ordering, arranging effect, along some specific guiding principle, on a key parameter like the lymphocyte counts.*

It is appreciated that the authors try to connect the angular gyrus to spiritual aspects of the experience, but this needs to be clarified in the Introduction as well. On the other hand, the authors state: *Thus, the brain area involved in the correlation described above (gyrus angularis) could also be linked to the “Aha! moment”.* Why is there suddenly discussion about an Aha moment when this has not been discussed before and there is no mention of it in the methods or results? This should probably be deleted.

Can the authors clarify why there were few significant findings? Perhaps it would be better to discuss the meaning of the lack of significant findings.

The entire last part of the Discussion beginning with the paragraph that starts: “When one is examining the effect of the Word of God on man,...” seems to be speculation, theology, and not based on the scientific results presented. This whole section should be deleted.

While the goal of the authors is appreciated, it seems that the limitations of the article described above are substantial.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

No

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Neuroimaging, meditation

I confirm that I have read this submission and believe that I have an appropriate level of

expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 21 Feb 2022

András Béres, Kaposi Mor Hospital, Kaposvár, Hungary

First of all, thank you Andrew Newberg for accepting our invitation and becoming the first to openly peer-review this paper. Thank you for going through the article so thoroughly with us.

This is to confirm that yes, it is the correlation between change in lymphocytes, and difference in activation between the active and the scientific control block that was significant (not between the active and the silence block; the abbreviation "s" refers to the "scientific text" 's block).

This is also to clarify that main purpose of the study was to measure the potential immunological effects of personal interventions that are primarily intended to elicit positive emotions at the bedside, among patients lying in the hospital. In the everyday practice of a hospital, this practically translates to visits by artists for the child-, and by chaplains for the adult population. This explains why we can refer to these two, seemingly different interventions on the same page in this study. "SHoRT" Study examined the effect of artists among sick children, "HEALING" Study examined the effect of a chaplain among sick adults.

The methodological challenge was that genuine meetings with chaplains in hospitals always contain a spontaneous ("inspired") element, the very creation of such authentic meetings is always based on the chaplain's intuition, and this spontaneous element has a major effect on the whole meeting - and hence on any immunological imprint, would there be any. This spontaneity and the large room left for the chaplain's inspiration reflects the original setting of the biblical times in which the "Word of God" was firstly said, when such meetings happened as a spontaneous act of the participants - i.e., this is how Jesus met people. Had we taken this spontaneous element out, we would have suffocated the very phenomenon of which we were trying to estimate the potential immunological imprint.

This methodological decision to leave the spontaneous element in, does not affect the reproducibility of the study - to the contrary, by proposing the possibility of the meeting for EVERY patient available on a ward on the day of the measurement, by establishing a rough order for the visits ("HEAL Score") to help manage the time available, but by always leaving to the chaplain the final choice of the patient she intends to visit, and only asking the chaplain to include the same biblical passage in every spontaneous meeting: these are the ways this study proposes to be reproducible anytime and anywhere in the world.

The question raised was whether meetings with a chaplain can elicit immunological changes in patients, IF these meetings are left as authentic, as spontaneous as they originally are.

It is the determination of a concrete group of patients among which to choose, the instruction for the chaplain to remain spontaneous and the permanence of the concrete biblical passage read that are fixed.

In contrast to the previous studies on praying and meditation, the main phenomenon that this study was focused on was the effect of a spiritual meeting - a meeting with the chaplain and through her, with the "Word of God". Thus, the phenomenon in focus in this study was not praying, but meeting.

It is the religious sensibilities raised by the topic touched by this measurement, and to avoid any potential distortions in the interpretation of the results that we found, that we felt obliged to include the theological viewpoint in the discussion of the results. I.e. the reader - believer or atheist - could later ask: WHY have we not measured more immunological changes, if the "Word of God" is believed to heal? And, if lymphocyte counts are correlated with an area of the brain involved in understanding words, does that mean that those who TRY to understand the biblical passage better, will have more healing lymphocytes? These are theological questions.

Thank you for being with us on this journey.

We hope that these clarifications will prove to be meaningful for you. We believe these are also the main topics the readers will possibly face while summing the article up in themselves.

Based on the Editorial Team's suggestion, we will be waiting for additional peer review reports before starting on the article revisions, in which we will address all the issues raised in full detail. We hope these improvements will render the article acceptable for you.

Competing Interests: No competing interests were disclosed.

Author Response 17 Mar 2022

András Béres, Kaposi Mor Hospital, Kaposvár, Hungary

We are now publishing a revised version (v3) of our article, in order to address your report in full detail.

To this we would add that the Isaiah chapter was expected to be less known by the participants, since it is seldom quoted and most of the enrolled patients were not actively practicing their faith; the proposition raised in your report, to use a different control as neutral, and to read from some other passage of the Bible such as a listing of names, is very interesting.

A potentially surprising twist to this idea is that such a list of names, as neutral as it seems to be from a grammatical point of view, is not neutral from a spiritual point of view. Indeed, central in Judaism and in Christian piety is the assumption that the *whole* Bible - and not just parts of it - is sacred, the emotionally exuberant and the less spectacular verses alike. Interestingly, then, even the listing of names could hold a deeper meaning in this context: in line with Hellinger's theory stating that our "self" cannot be conceived as an individual being, but our subconscious is deeply rooted in the soul of our family, that of our ancestors, in the wider sense of the whole family of mankind (1, 2), the recitation of ancient names is portent of deep memories, thus can be evocative, and has the potential to move the

deepest layers of the collective subconscious.

The interesting question is whether these potential effects can be measured with fMRI, and whether this additional spiritual content would only be perceived by the religious participants, or some unintended imprints would also be detectable among the atheists. What do you think?

In the current measurement, the usage of a text without any spiritual content as control seemed more appropriate, to maximally differentiate it from the biblical reading used in the active block.

The comparison of biblical passages with different emotional content during fMRI, as well as the more sensitive measurement of the immunological parameters (by means of flow-cytometry for example, a tool that we could not afford due to financial constraints) are lines along which further research could develop - but this already paves the way for a series of completely new measurements.

References

- (1) Hellinger B: *Rachel Weeping for Her Children: Family Constellations in Israel*. Heidelberg, Germany: Carl-Auer-International; 2003.
- (2) Hellinger B: *Peace begins in the soul: Family constellations in the service of reconciliation* (C. Beaumont, Trans.). Heidelberg, Germany: Carl-Auer-Systeme Verlag; 2003.

Competing Interests: No competing interests were disclosed.

Author Response 17 Jun 2022

András Béres, Kaposi Mor Hospital, Kaposvár, Hungary

Dear Andrew B. Newberg,

We are now publishing a further revised version of the article "Healing through faith: meeting a chaplain coupled with biblical readings could produce lymphocyte changes that correlate with brain activity (HEALING study)", in order to fully address the concerns you articulated regarding Version1.

Introduction

Based on your advice, we have now clarified what our hypotheses were, what we were expecting to find in regards of changes in the immune response and the involvement of which brain areas could be anticipated. The truth is we intentionally started this clinical trial with as few preconceptions as possible, to remain open to any significant correlation that could emerge between the parameters we could afford to measure in a clinical setting – some of which are traditionally considered to correspond to the body, some others to the soul. Our measurement is a pilot study in this respect.

Methods

We have further clarified why the subjects were not randomized by chance, but by convenience i.e., depending on the availability of the chaplain on the days of the measurement (when the laboratory staff was available for the extra measurements and when the fMRI equipment could be used for the study). Allocating by chance would not have been a difficult option technically but could have resulted in significant distortions in the supposed psycho-immunological effects. Indeed, by the time the patients were classified as eligible and randomizable in this study, they represented this tiny portion of patients who were truly in need of a visit by the chaplain. The cancellation/postponement of the visit could have resulted in significant stress, disappointments, by which means the measurement method would have disproportionately influenced the parameters measured in the control group.

In the intervention group, it was the chaplain who decided whom she wanted to visit among the patients who were randomizable. In the Discussion, we explain in detail why we opted for this methodological decision – the main goal was not to interfere with the genuine, authentic character of the chaplain-patient relationship that we were aiming to understand, and that always contains such a spontaneous element.

The timing of the blood collections (30 minutes prior, and 60 minutes after the meeting) is now explained, it was based on the similar intervals used by previous, basic psycho-immunological studies that served as our starting point and that are mentioned in the Introduction (especially Berk et al., Bennett et al., Matsuzaki et al.).

We believe the Isaiah chapter we used is, although not an entirely neglected, but a rarely used passage in religious practice, moreover, most of the patients enrolled were not actively practicing their faith. As to the usage of another biblical passage such as a listing of names for neutral control, we refer you back to our response in Version3 – even “neutral” passages can be portent of a “numinous” component. The contrast between a sacred passage intended to offer comfort, and a medical text with potentially fearful connotations was more marked, and therefore helped bring out the potential differences better.

Part I Results

Based on your suggestions, we have now significantly simplified this section and moved all the figures and tables containing null-results to the *Extended data*, so as not to overwhelm the reader with data that is non-significant. Also based on your suggestions we added data on effect size when there seemed to be a trend towards significance that might help developing further studies.

Part II Results

We have unambiguously clarified the meaning of the “a”, “s” and “c” abbreviations.

There were no general differences that could be unanimously detected among all the patients, between the active prayer block and the control block, so hearing a religious recitation did not affect the brain differently than a neutral/scientific recitation, unanimously for all the patients enrolled in this study – but the main finding of the study is

that a significant correlation between lymphocytes and brain activity emerged with the active minus scientific control block. This finding totally echoed previous psycho-immunological findings and is now highlighted in the Discussion.

We hope your assessment of the statistical analysis being not appropriate was related to the confusing presentation of the null results, and that this issue is now fixed. The statistical tools used for interpretation, especially for fMRI evaluation are detailed in the Methods section and the Results part now is now limited to the precise description of the positive findings with some careful allusion to possible trends. We added the r value for the main correlation found.

Discussion

We left the reference to Salopek's *"Out of Eden Walk"* in the Discussion but put it to the end of the first part, to show that this reference is meant to clarify the methodological decisions of the authors – a constant effort to produce authentic encounters at the bedside or in the chapel, even at the cost of a very slow pace of enrollment. We further illustrate this concept with the example of two patients whom we enrolled by proactively trying to overcome the special difficulties raised by their disabilities. Only a very personified study design could allow for this.

Also, the term "auto-control" setting is now clarified in the text.

It is particularly important that patients' individual results are first compared to their own baseline values (difference in their own activation patterns during intervention and silence; difference in their own lymphocyte counts), in the context of a study using a cohort design, with many different patients enrolled.

The SHoRT trial is used for comparison in the Discussion because either the artistic interventions for hospitalized children or the spiritual interventions for hospitalized adults were originally implemented in clinical practice with the implicit intent to elicit positive emotions among patients, to alleviate the burden caused by the disease. This is now explained in the Introduction, and based on your suggestion, the revised Introduction has been considerably enriched with additional key articles on positive emotions and immune function. These additional references help understand why the current study needed to put so much emphasis on proper patient selection, authenticity of the interventions; they also put the current study's sample size, measured immune parameters, obtained p values, direction of change (increase or decrease) in perspective, as compared with similar basic studies.

The revised Introduction also points towards a more nuanced approach to the visits by a person of faith, with a highlight on the religious undertones, and the revised Discussion also elaborates on that the intervention originally designed to elicit positive emotions, may have resulted in other emotions as well. The lymphocyte changes in the subgroup who received communion gives a striking example. The „Healing questionnaire" designed to record rough psychological aspects of the meetings, like emotional depth, perceived turmoil, correspondence with the chaplain as assessed by the participants... shows lines for further research, but the amount and length of questionnaires needed to be considerably

restrained in the current setting, so as not to overwhelm the patients with documents to be completed - that could have interfered with the meetings themselves. As the Discussion acknowledges, the different emotional aspects of the spiritual experience in hospitals will need further research.

The concept of a "guiding principle" having an arranging effect on the lymphocyte counts is now clarified in the Discussion.

Based on your suggestion, we clarified in the Introduction how the angular gyrus could be involved in the spiritual experience, so that its appearance in the Discussion does not come across as a totally unexpected finding. Also based on your suggestion we deleted the allusion to the 'Aha moment' from the Discussion (correlations are possible but seem too remote to be dealt in detail in the Discussion of this study).

Finally, although we keep the final part of the Discussion for the theological perspectives, we'd like to highlight that this section is called "Excursus". We think it is always interesting to see how empiric observations relate to the way theology thinks about God. This is not meant as a substitute to replace the scientific discussion, but a way to complement it.

We hope that with these significant revisions in the Discussion, your assessment regarding the conclusions as not having been drawn as adequately supported by the results is now changed.

We are honored by your accepting to review this study. We honestly appreciate your reviewing it so thoroughly and hope our revisions have sufficiently addressed your concerns so that you now find the article acceptable from a scientific perspective.

Competing Interests: No competing interests were disclosed.

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