University of Wisconsin
SCHOOL OF MEDICINE
AND PUBLIC HEALTH

Department of Psychiatry

December 31, 2016

Faculty of Psychology Board
University of Warsaw
Stawki 5/7
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Dear Faculty of Psychology Board:

I am an Associate Professor in the Department of Psychiatry and the Department of Medical Physics at the University of Wisconsin – Madison, and I was asked to serve as an outside expert and external examiner for the Ph.D. Thesis of Anna Rita Egbert.

The Ph.D. Thesis from Anna Rita Egbert, entitled "The effects of aging and HIV infection on the relationship between the Resting State of the brain and neurocognitive function," investigates the relationship between age and both resting-state brain connectivity and cognitive function in a group of individuals with HIV in comparison to an HIV negative control group. More specifically, this study also examines the interaction between age and HIV status in its relation to the brain's resting-state activity, functional connectivity, and cognitive function. Resting-state brain function is assessed using several different approaches – a seed-based functional connectivity using regions of interest derived from a prior study by Dosenbach et al.; an independent-component analysis; the amplitude of low frequency fluctuations (ALFF); the regional homogeneity (ReHo) of the signal; and scaled versions of the latter two measures. This thorough study finds 1) significant correlations between age and various measures of resting-state brain function in the HIV negative control group, consistent with prior studies of normal aging; 2) significant differences in resting-state brain function in the HIV positive compared to HIV negative group; and 3) significant interactions between age and HIV status in its relation to resting-state brain function. Furthermore, this study revealed significant relationships between these differences in resting-state brain function and certain cognitive measures. The findings within this thesis work provide evidence of compensatory mechanisms in the aging of individuals with HIV, and support a model of accentuated rather than accelerated aging in individuals with HIV.

This thesis work is the result of a successful international collaboration between different centers in Poland and the New Jersey Institute of Technology (NJIT). Data collection was achieved at the Bioimaging Research Center (BRC) in Kajetany near Warsaw, Poland. The analysis of the structural and resting-state functional MRI data was performed at the Department of Biomedical Engineering at NJI, in close collaboration with the BRC, under the mentorship of the internationally renowned expert in resting-state fMRI, Dr. Bharat Biswal. Ms. Egbert's successful thesis work clearly shows the benefits that can be achieved by melding the diverse expertise (HIV, aging, and fMRI) at each of the different international centers.

Ms. Egbert's thesis work is an important contribution to our understanding of the cognitive and brain alterations in individuals with HIV during the process of aging. While there are an increasing number of

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studies of brain function, including resting-state functional connectivity MRI, in both aging and HIV, there have been relatively few studies that have examined the interaction of these two factors. A particular strength of this study is the large sample size of 108 participants (54 HIV+, 54 controls). An additional strength is that comorbidities were tightly controlled. While Ms. Egbert does acknowledge in the discussion section of this thesis that this constraint may be a limitation in that only the most "healthy" HIV+ individuals were studies, it does make it easier to conclude that the observed findings are associated with HIV rather than a comorbidity. The findings of the relationship between age and resting-state brain measures in the control sample matches well with prior literature, which provides more confidence in any differences observed in relation to HIV status.

The methodology used to analyze the resting-state fMRI data are sound and uses currently accepted processing steps. It is particularly good to see that steps were taken to minimize the influence of head motion, such as censoring motion-corrupted time points, since this has been a topic of considerable attention and concern in recent years.

Overall, the thesis is very well written, well organized, and easy to follow. One of the challenges in this thesis work is that there multiple imaging measures and a large number of cognitive measures resulting in a large number of possible associations and findings. The discussion section, however, does a very nice job in leading the reader through the various findings. For example, the discussion of the aging findings nicely matches the results to prior literature. The discussion of the HIV resting-state findings also does a very nice job highlighting the similarities to prior studies and providing potential reasons for discrepancies with prior literature.

The main weakness with this thesis is that it would have been helpful to have more motivation for why the different functional connectivity metrics were evaluated. The various metrics (e.g. seed-based connectivity, ICA, ALFF, ReHo) do capture different important aspects of the signal, and there is certainly value in looking at all of these measures. However, without a clear explanation of what these different metrics are intended to capture, there is a danger that this approach can be seen as testing multiple metrics in the hopes that at least one of them will show a significant difference. If this is indeed the intended approach, then one should perform additional multiple comparison corrections to correct for the large number of imaging metrics and cognitive measures whose association was evaluated.

There are a few additional minor weaknesses. Most of the HIV+ participants were on medications, which makes it more difficult to parse the effects of HIV versus medication. However, it would be difficult to recruit participants not on medication, so the experimental design used in this study is unavoidable. As mentioned above, head motion can significantly affect functional connectivity estimates. A recent study by Eklund et al., which has received considerable attention in the popular press, showed that false positive rates in fMRI studies can be significantly inflated using several of the popular fMRI analysis packages. In response to this article, the AFNI developers have incorporated a modification to the cluster-based multiple comparison correction which more accurately estimates the likelihood of false positives (by estimating the autocorrelation function for each subject). It is unclear

whether this more recent approach was used in this thesis work. A number of approaches were used in this study to minimize the impact of motion, such as image registration and censoring time points corrupted by motion. However, since increased left-right connectivity fits with both the HAROLD model and with greater motion, it would be good to check whether the subject head motion is significantly correlated with either age or HIV status, in order to rule out the possibility that residual motion-related signal changes could be responsible for these findings.

In summary, this thesis work is a well-executed and well-presented scientific study that adds important new knowledge about the brain's functional and cognitive changes with HIV and aging. In my professional experience, this thesis clearly fulfills the standard requirements for a Ph.D. thesis.

Best regards,

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