REPORT OF RESEARCH RESULTS

Title: "Enhancing Exercise-mediated Longevity and Brain Function in the Elderly"

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Summary

This study investigated the effects of physical and mental activities on physical and mental health (and hence successful ageing) in 120 Singaporean older adults aged between 55 and 70 years. These older adults who were not already engaging in regular exercise (three hours of moderate-to-high intensity exercise) were randomly allocated to one of three groups:

1) **Group Exercise** in which participants underwent 12-weeks of thrice weekly one-hour moderate-to-high intensity physical activity sessions comprising aerobic (sustained cardiovascular activity in the 60-80% range of maximum heart rate) and strength components; or
2) **Group Toning** in which participants underwent 12-weeks of thrice weekly one-hour very low intensity physical activity sessions comprising "non-aerobic" (i.e., activity below 60% of maximum heart rate) components without any strength (e.g., additional weight bearing activities); or
3) **Group Sedentary** in which participants simply maintained their relatively sedentary lifestyle (baseline control group).

A range of research methodologies was employed including: neuroimaging (MRI and fMRI), neuropsychological and cognitive test batteries, cardiovascular reactivity, psychosocial, quality of life, psychiatric, physical fitness, and physiological stress (cortisol) measures which were taken before and after the 12-week intervention period to assess the impact of these interventions relative to the baseline control.

The results indicated that, relative to both Group Sedentary and Group Toning, Group Exercise benefited in terms of brain function (fMRI), cognition, quality of life, depressive symptoms (assessed via clinical interview), physiological stress (cortisol) from pre- to post-intervention. These improved measures were paralleled by improvements in physical fitness (i.e., increased aerobic capacity and decreased BMI). Participants in Group Toning, who would have been exposed to social interactions and support via their peers, and thus engaged in peri-session mental and social stimulation (as would have those participants those in Group Exercise) expressed improvements in self-rated depression symptoms and physical fitness relative to Group Sedentary (who would have not experienced these additional social interactions and support. These self-rated "improvements" in Group Toning were not however found to be reliable in the clinical interviews about their depression symptoms, and there were no other benefits (e.g., in terms of cognition, brain function) and from this apparent social and mental stimulation.

In terms of hormones, we found that Group Exercise experienced reductions in cortisol relative to both Group Toning and Group Sedentary. In Group Exercise, the reduced cortisol measures were associated with reduced clinical symptoms of depression and in terms of brain activity: increased hippocampal brain

activity and reduced amygdala brain activity. Other hormone factors are awaiting processing, but we anticipate similar findings based on the initially processed cortisol tests. These relationships may help elucidate the role of physiological stress in causing adverse effects on brain function. Increased cortisol, and reduction in hippocampal volume has been associated with mental health problems such as depression or post-traumatic stress disorder, and poor quality of life. Increased amygdala activity is associated with clinical depression and anxiety.

In conclusion, physical exercise appears to reduce levels of physiological stress (reducing stress hormones such as cortisol) and appears to confer a direct benefit on brain function (in terms of increased hippocampal brain activity and improvements in cognition, memory, mental health and quality of life). These results are novel, ground breaking and are expected to create high-impact in the scientific community.

The results have been of direct interest to those interested in population health and health economics. For example, as a result of this research I have begun discussions with the People's Association (Active Ageing Programme) and other national or community based centres to help Singaporeans age more successfully. In terms of media attention, aspects of this research have featured in the Straits Times newspaper and a Discovery Channel programme ("Inside Out"). I have also been invited to speak at several international conferences about this research.

Aim of Research

We aimed to show that physical activity can stem the onset of age-related decline in neuroplasticity by exploring physiological and neurocognitive effects of various types of exercise intervention on brain function. In order to delineate the mechanisms underlying exercise-mediated brain function changes, we investigated the levels of various hormones pre- and post- exercise and examined how they relate to changes in the brain (both structural and functional). These biomarkers could then be used as indicators of neurogenesis and synaptic plasticity. Coupled with structural and functional MRI neuroimaging analyses this provided further help in understanding the changes in the brain that accompany exercise.

Method of Research & Progression

We conducted studies of exercise training and measured changes in brain function during tasks relating to executive functioning and memory in older adult participants. These measures included physical fitness assessments, neuroimaging, memory and other neuropsychological tests, clinical assessments of mental health, quality of life, and circulating levels of hormones and growth factors (e.g., cortisol and vascular endothelial growth factor), and were intended to help understand the mechanisms underlying exercise-mediated changes in brain function.

By the end of the study we had sampled 120 English-speaking healthy older adults (aged 55-70 years) in whom all measures were recorded pre- and post- intervention. The participants were randomized to different groups, each having a different intervention. These interventions were different types of exercise (e.g., aerobic sessions or fartlek training) or appropriate control activities (e.g., stretching or light walking). Interventions sessions lasted 60-minutes per session and were conducted three times per week for the study period of 12-weeks. The intensity levels of the exercise were carefully monitored during the intervention sessions to ensure safety and the appropriate amount of exertion.

We conducted several cognitive tasks to assess for example the participants' level of executive functioning using a modified Wisconsin Card Sorting Task (Cognitive Set Shifting Task) which also formed part of our event-related fMRI brain function analyses. Another test included the memory encoding and recognition test which involved a series of pictures presented to the participants during their fMRI brain scanning session, followed by another batch of pictures from which the participant was required to recognise those which had been previously presented before. Blood samples were also collected from our participants to assess their hormone levels using ELISA enzyme immunoassay kits. A 3T Siemens Magnetom trio MRI scanner with a 32-channel radiofrequency coil was used for structural and functional MRI brain scanning measurements. For fMRI analysis, we used the echo-planar imaging (EPI) sequence with blood oxygenation level dependent (BOLD) contrast. T2*weighted images were collected from the participants (TR = 3000ms, 42 slices of thickness 3.0mm) and co-registered with the high resolution T1-weighted MPRAGE anatomical images. After preprocessing (motion correction, linear smoothing, and Talairach transformation) we calculated the random effects general linear models (BrainVoyager) and voxels above threshold (corrected p<0.05) were considered significant.

Results of Research

As mentioned in the earlier sections, 120 sedentary healthy elderly volunteers (mean age 60, range 55-69 years, 50 males) took part in 12-week controlled trials in which they were randomized to one of three interventions – sedentary control (lifestyle unchanged), toning/stretching (non-aerobic), and exercise (aerobic) training. Changes in participants' levels of physical fitness, anthropometrics, cognition, fMRI, psychosocial, and physiological functioning were assessed before and after the 12-week intervention by experimenters who were blind to the participants' group allocation (Graham et al., in preparation).

A priori contrasts revealed that Group Exercise significantly improved fitness levels ($F_{1,39}$=26.83, p<0.05) and reduced body mass indices between pre- and post-intervention time-points. QoL measures, in which participants were asked about their daily living activities, also improved but again only in the aerobic group ($F_{1,39}$=5.76, p<0.05). Cognitive status was measured using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) which covers five domains - Immediate Memory, Visuospatial/Constructional, Language, Attention, and Delayed Memory. Participants in the Aerobic intervention showed significant improvements ($F_{1,39}$=36.30, p<0.001) compared to the other groups (see Table 1) – particularly in executive function (semantic fluency), attention and working memory (forward digit span) which is consistent with past research (e.g., Colcombe & Kramer, 2003).

Table 1 Demographic profile, fitness, depression and RBANS scores across all groups (**p< 0.001)

Group	Aerobics	Stretch	Sedentary
Age (years)	59.1	61.0	59.4
Current IQ score	106	105	108
Level of education (years)	11.15	11	10.67
Number of subjects (Male:Female Ratio)	16 (4:12)	16 (4:12)	16 (4:12)
Pre-post-intervention improvements in fitness (correlates with VO_2max)	49.04**	-11.78	18.45
Pre-Post-intervention changes in Hamilton Rating Scale for Depression	-1.2**	-0.3	-0.2
Pre-Post-intervention cognitive improvement (RBANS)	6**	-5.06	-0.5

Participants were interviewed using the Hamilton Rating Scale for Depression (HAM-D) to assess the presence and severity of depressive symptoms (higher scores indicate greater severity of depression). Although the scores were too low to warrant clinical diagnosis of depression, our results show that aerobic training significantly reduced depressive symptoms. Such decreases in symptoms from pre- to post-intervention were not observed in the sedentary or non-aerobic stretching controls (see Table 1). Our results suggest that exercise has a direct benefit brain function rather than working indirectly (as had been previously speculated - e.g., via increased social activity as a form of distraction from negative thoughts e.g., Mead, et al., 2008) because similar reductions were not observed in the Toning/Stretching control group.

In one of the fMRI scanning sessions, participants viewed a series of 50 pictures and were subsequently asked to classify these 50 pictures intermixed with 50 new but similar pictures to those previously seen as either "old" or "new". Comparing only correctly remembered items, greater hippocampal activity was found post-exercise in the Aerobics/Exercise group compared to the other groups (see Figure 1B).

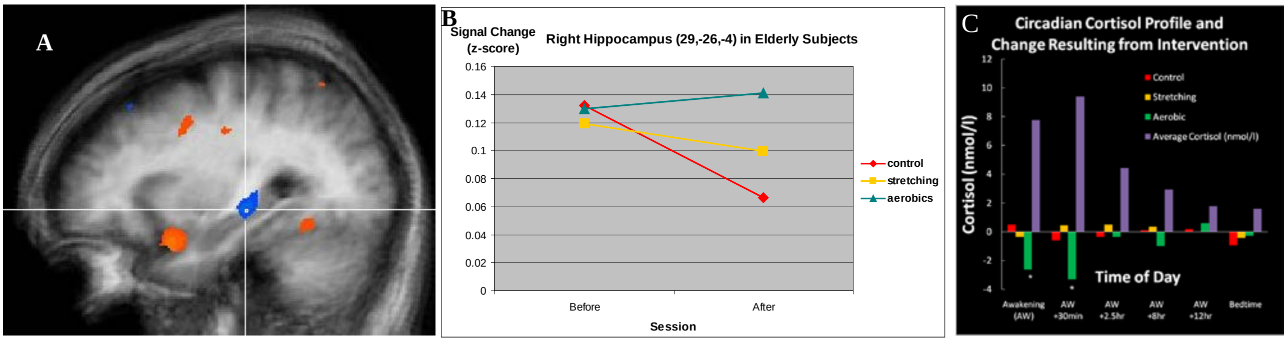

Figure 1 (A) Functional imaging of the hippocampus during a long-term memory recall task in healthy elderly subjects. (B) Elderly subjects in the Aerobic group maintained hippocampal activity in the recognition task as opposed to control and stretching groups who showed significant activity reductions across the intervention period. (C) Level of cortisol at different time-points in the day and the changes from pre-post intervention.

Consistent with an earlier study in older adults (Colcombe *et al.,* 2004) , our event-related WCST fMRI task showed that aerobic training increased activation in anterior cingulate (BA 32) and middle frontal (BA 10) gyri – regions associated with selection from competing response alternatives and manipulation of complex rules during decision making (Graham et al., 2009). More importantly, we were able to demonstrate increases in hippocampal activity in the Aerobics group. As far as we know we are the first group to demonstrate fMRI changes in the hippocampus and hence demonstrate changes in brain regions that parallel those found to be augmented by exercise intervention in animal studies. These changes in hippocampal activity in Group Exercise/Aerobics were associated with reduced levels of cortisol – especially at the early morning peak in the circadian rhythm (Figure 1C).

Future Areas to Take Note of, and Going Forward

With many developed nations facing high growth rates of their older adult population, there is an increasing awareness of the importance of physical exercise and a healthy diet in maintaining good physical health into later years. Despite this, few people actually achieve regular exercise, and many cite reasons such as lack of time, continual work and social commitments. This is reflected by the growing number of younger adults battling weight problems such as obesity. Recognising the important effects that exercise can bring for our health is one part of the solution. More is needed however to reinforce the formation of physical exercise and good nutritional habits in young and older adults. This could include incentives to adopt healthy life habits such as reduced health insurance premiums for those who can prove they regularly exercise and demonstrate high levels of physical fitness. In Singaporean males for example, for easy implementation this could be based on the regular fitness assessments as part of the national service requirements. This is a good time to start thinking of our personal health in terms of health maintenance and disease prevention. After all most car owners will happily invest in regular servicing and maintenance packages for their cars – why not think about our own health in this way too?

Means of Official Announcement of Research Results

There are two major sources here of publicity for MSIG. First, to date I have been invited to give two keynote presentations about this work. These were international conferences held at NUS, and acknowledged MSIG in my final “acknowledgements” slide which was displayed throughout most of the question time after my talk. Secondly, we have collected a very large amount of data and are still preparing the publications of our research findings. We will of course acknowledge MSIG when our top-tier internationally reviewed journal articles (e.g. published in Proceedings of National Academy of Sciences, USA) are published shortly after they are accepted. The review process for top-tier journals is usually a long process and can take several months or a year.