

**Final Report to the Centre for Ageing Research and Development in Ireland
(CARDI) 21st May 2010**

Title of project: Using aerobic exercise to promote brain plasticity and increase functional capacity in older people.

Investigators:

Professor Richard Carson: *Queen's University Belfast*

Dr. Madeleine Lowery: *University College Dublin*

Prof. Giuseppe De Vito: *University College Dublin*

Dr. David Craig: *Queen's University Belfast*

Dr. Brian Caulfield: *University College Dublin*

Dr. Katherine Johnson: *Trinity College Dublin*

Dr. Áine Kelly, *Trinity College Dublin*

Scientific Aim of the Project:

To investigate the role of aerobic exercise in promoting brain plasticity, a process that encourages independent ageing and recovery from neurological illness.

Executive Summary:

We assembled an inter-disciplinary (geriatric medicine, exercise science, biomedical engineering, psychology, physiology) all-island team of scientists and health professionals to assess whether brain plasticity, as induced by non-invasive cortical stimulation techniques, is enhanced in older people following aerobic exercise. While this was a very small-scale research project, it nonetheless demonstrated the feasibility of conducting collaborative research of this type in an all-Ireland context. The scientific outcomes indicate that older people exhibit changes in brain plasticity in response to cortical stimulation that are similar in character to those shown by young adults. The potential role of aerobic exercise in promoting brain plasticity however, presently remains equivocal.

Achievements of the Project in Relation to the Aim and Objectives of the CARDI Grants Programme

Aim of the CARDI Grants Programme

- To advance the ageing research agenda in Ireland, North and South

Objectives of the CARDI Grants Programme

- To support and enable cross-border and inter-disciplinary research collaboration on ageing and older people
- To stimulate research activity on the needs of older people within a policy and practice context in Ireland
- To increase the capacity of the ageing research community in Ireland

1) Support and enable cross-border and inter-disciplinary research

The award of the Research Grant provided a substantial impetus to the formation of a collaborative network involving scientists and clinicians North and South. In concrete terms, the development of the network was manifested as follows.

The collection of primary data took place in Belfast. In this local context, the project promoted a new collaboration between Prof. Richard Carson (QUB: School of Psychology) and Dr. David Craig (QUB: School of Medicine). This inter-disciplinary linkage was the foundation for a successful application for funding made subsequently by Prof. Carson and Dr. Craig to Northern Ireland Chest Heart and Stroke, to support a project that will focus on brain plasticity in stroke survivors. In so much as the prevalence of stroke is markedly greater in older people, this derivative research will also advance the ageing research agenda in Ireland.

Our research protocol involved the administration of an aerobic exercise regime that was tailored individually to each participant. Training in the delivery of this protocol was provided to Dr. Mary Hanley – a research assistant who contributed to the project, and Mr. Barry Nelson – a Ph.D. candidate at QUB who played a

significant role in its delivery, by Prof. De Vito (and Dr. Romain Cres) at the School of Physiotherapy and Performance Science at UCD, in conjunction with Brian Caulfield. As it is envisaged that Mr. Nelson will extend this line of research in the course of his Ph.D. program, further close collaboration with Prof. De Vito's research group at UCD is anticipated.

Dr. Katherine Johnson (initially TCD, subsequently QUB) and Dr. Áine Kelly (TCD) provided the principal input to the project in relation to the protocols for DNA extraction and genotyping. All of the study participants have provided samples, however the DNA extraction and genotyping, which will initially be with respect to Brain Derived Neurotropic Factor (BDNF), can only be undertaken economically in large batches (i.e. 50 or more samples simultaneously). As such, we expect that the most substantive benefits of this part of the collaborative network will shortly be manifested.

Although Prof. Richard Carson (QUB) and Dr. Madeleine Lowery (UCD) had an existing collaborative research agenda, the current project has served to further consolidate this cross-disciplinary (biomedical engineering / neuroscience) linkage and has generated a number of new avenues for research, particularly in the area of stroke rehabilitation. Presently Prof. Carson and Dr. Lowery are focussing on the analysis of the electrophysiological data generated in the present project.

2) To stimulate research activity on the needs of older people within a policy and practice context in Ireland

In undertaking the research project it was necessary to confront a number of practical challenges, particularly in relation to the recruitment of participants to the study. While a number of steps (outlined below) were taken to overcome these challenges in the local (i.e. Northern Ireland) context in which the collection of primary data took place, we believe that the experience thus acquired has

more general implications with respect to the conduct of research that focuses on the needs of older people.

The first phase of recruitment involved visiting 21 golf clubs around the Greater Belfast area and placing adverts on the notice boards inviting people to contact the research team if they were interested in taking part. In the second phase, Dr Hanley and Mr. Nelson gave a presentation to approximately 350 people, many of whom were in the target age-range, enrolled in "World Literature" - an Open Learning short course offered at Queen's University. We also occupied a stand at the "Young at Heart" exhibition in Belfast. A total of 104 (stamped and self-addressed) information packs were mailed to individuals who through these initial phases expressed an interest in participating. Of these 46 completed information packs were returned.

The information pack contained a medical history questionnaire. With respect to the 46 questionnaires that were returned, 11 individuals were automatically excluded from receiving non-invasive cortical stimulation on the basis of pre-defined criteria (e.g. a history of head trauma/ a family history of epilepsy). Nine other individuals able to receive cortical stimulation were excluded from the study due to contraindications to the exercise component (e.g. they had experienced heart palpitations or skipped beats). These individuals were informed that they were unsuitable for the current investigation, however they have all indicated that they would be happy to participate in a future study that will be undertaken by Mr. Nelson as part of his Ph.D. research.

All of the remaining participants were telephoned and asked questions related to their habitual levels of physical activity (Appendix 1). These responses were noted and sent along with the completed medical history questionnaire to Dr. Craig for further screening. At this stage, 6 further individuals were excluded, either because Dr Craig deemed that their habitual levels of activity were too low to permit the exercise protocol to be undertaken, or because they were taking

medication that precluded their participation. In the event that an individual presented with a blood pressure reading of greater than 140/90, inclusion in the study was permitted only following further clinical examination.

We believe that it is worth highlighting at this stage, some barriers to the conduct of research activity on the needs of older people that were encountered in the course of the present project. In large part these were related to issues of research governance at the institution that hosted the collection of primary data. Our original intention was to assess blood levels of BDNF pre- and post-intervention, and to also use these samples to extract DNA for the purposes of BDNF genotyping. To this end, Mr. Nelson undertook a training course in phlebotomy. Subsequently we obtained advice from the Research Governance Office at QUB that blood samples could only be taken in specially configured rooms in a clinical facility. While this is not to our knowledge a statutory requirement, it precluded the use of blood samples in the present study. As an alternative means of conducting the genotyping, we therefore opted to use saliva samples for the purpose of DNA extraction. A protracted period of communication with the School of Psychology Research Ethics Committee and the Research Governance Office at QUB was then necessary to address concerns raised in relation to the potential status of saliva as a “human tissue sample”. It was an additional requirement of the ethical approval granted to the project that all sessions that engaged older adults in exercise protocols must take place in an environment in which clinical cover is available. Fortunately Dr. Craig was able to arrange access to a testing room in the Whitla Medical Building at QUB, however the requirement for on-site clinical cover imposed significant restrictions on the testing schedule.

3) To increase the capacity of the ageing research community in Ireland

In addition to the increase in capacity brought about by the collaborative research network established via the project, both Dr. Mary Hanley – the research assistant who contributed to the project, and Mr. Barry Nelson – the Ph.D.

candidate who played a significant role in its delivery, gained invaluable new experience in the conduct of research with older people. In addition, Mr. Nelson will be building upon the present research project in the course of his Ph.D. program, and will extend our original objectives by also seeking to assess the role played by *habitual* levels of physical activity in determining brain plasticity in older persons.

Implications for Policy

As this was a very small-scale research project, and accordingly the findings preliminary, it would be inappropriate to suggest that the results carry direct implications in terms of policy for older people. The outcomes that have been obtained thus far do however suggest that that older people exhibit changes in brain plasticity, in response to at least one mode of cortical stimulation, that are similar in character to those shown by young adults. The potential role of aerobic exercise in promoting brain plasticity presently remains equivocal. Since to the best of our knowledge the present study is unique, and the size of the relevant effects is therefore unverified, it would be premature to conclude that aerobic exercise does not play a role promoting brain plasticity and functional capacity in older people.

Summary of Scientific Outcomes

Abstract submitted to the Society for Neuroscience for presentation at the annual meeting in San Diego in November 2010.

Title: The effect of acute exercise on neural plasticity.

Authors: B.D. Nelson, D. Craig, G. DeVito, K.A. Johnson, M.M. Lowery, Á.M. Kelly, B.M. Caulfield, M. T. Hanley & R.G. Carson.

The aim of this study was to determine the effect of acute aerobic exercise on the impact of a subsequent plasticity-inducing protocol that has been shown previously to increase the excitability of corticospinal projections to muscles in the arm. A group of healthy participants (aged 21-80) undertook two 30-minute sessions of Paired Associative Stimulation (PAS), whereby a train of electrical stimulation (1ms pulse width, 10Hz, 500 ms duration) was delivered to the right Flexor Carpi Radialis (FCR) motor point, followed 25 ms later by a TMS (Transcranial Magnetic Stimulation) pulse delivered to the left primary motor cortex (M1). This was repeated every 10 seconds for thirty minutes (total 180 pairs). In one session, PAS was preceded by a 30-minute period of cycling on a stationary bike. The intensity of the exercise was personalised to each participant on the basis of a previous ramp-type test, in which the heart rate was measured at differing levels of load. A regression (intensity v heart rate) was performed to establish the intensity that corresponded to the maximum predicted heart rate. The participants cycled at 50% of this intensity during the experimental session. In the control (non-exercise) session, the participants sat quietly for 30 minutes. Measures of corticospinal excitability were obtained on six occasions during each session: at the beginning, after the exercise (or after 30 minutes at rest in the control condition), and at 0, 10, 20 and 30 minutes following the cessation of the PAS. Planned comparisons of means based on an ANOVA design, revealed that in both the exercise and control sessions, the PAS protocol gave rise to reliable increases in corticospinal excitability ($p < 0.03$). It did not appear to be the case that the prior exercise protocol had a reliable impact on the magnitude of these effects. The present findings, while preliminary, suggest that a preceding bout of moderate intensity aerobic exercise does not impact upon metaplasticity, at least in relation to interventions that alter the excitability of corticospinal projections to muscles in the forearm.

Scientific Methodology

Recording procedures

Electromyographic activity (EMG) was recorded from the flexor carpi radialis (FCR) and extensor carpi radialis (ECR) of both arms. The signals were amplified (x2000) and digitised (sampling rate 4000Hz). The data were recorded using signal software and a micro1401 (CED) and stored for later offline analysis.

Measure of Cortical Excitability

Motor evoked potentials (MEPs) were elicited by delivering magnetic stimuli to the left motor cortex (M1) using a figure-of-eight coil (internal wing diameter 55mm) connected to a Magstim 200 stimulator (Magstim, Dyfed, UK). The hotspot was determined as the optimum position over left M1 for eliciting MEPs in the FCR muscle where suprathreshold TMS consistently produced the largest MEPs. This was marked with a soft felt-tip pen. Once the hotspot had been determined the coil was held in place using a coil holder (Magstim) with the handle pointing backwards at approximately 45° to the sagittal plane so that current flow was induced in a posterior to anterior direction over the motor cortex. Resting motor threshold (RMT) was determined as the lowest stimulator intensity at which a motor evoked potential (MEP) between 50µv and 100µv was obtained in 5 out of 10 trials. Recruitment curves were obtained by randomly delivering 6 TMS pulses at 10 different intensities (from 70% to 160% of RMT in 10% steps; total 60 pulses). A measure of the excitability of the corticospinal pathway was derived from peak-peak amplitude of the MEPs.

Paired Associative Stimulation (PAS)

This was the key intervention employed to induce cortical plasticity. The technique involved delivering a train of electrical stimulation (1ms pulse width, 10Hz, 500ms duration) to the motor point of the right FCR followed 25ms later by a magnetic pulse delivered to the left M1. The electrical stimulation was delivered

at the intensity at which a minimal contraction could be observed in the FCR tendon. The magnetic stimuli were delivered at 120% of RMT.

Ramp-Test Session

A heart-rate monitor was attached to the participant. Their height and weight were measured. Using these values, along with the gender and age, a calculation of the estimated max power at which they could cycle was obtained. Based on this value, participants were required to cycle for 4 minutes at 20%, 40% and 60% of their estimated power max with a one-minute rest period between the different intensities. The resting heart rate was recorded. Measures of heart rate were also taken every minute, and a further 3 times during the last minute. The last 3 measures of heart rate were taken and plotted against the intensity (in watts) that the participant was cycling at. From this an individualised graph of heart rate vs. intensity was obtained from each participant. The estimated maximum heart rate was established for each participant based on the formula $(217 - [0.85 * \text{age}])$. Fifty percent of the intensity that corresponded to maximum heart rate was taken as the intensity for the experimental session.

Experimental session.

The participant was seated in a modified dentists chair with their arms in a semi-pronated position. The flexor carpi radialis (FCR) and extensor carpi radialis (ECR) was located in both arms and marked with a soft-felt tip pen. A bipolar electrode connected to a constant-current square wave stimulator (digitimer) was used to locate the motor point on the right FCR muscle. A topical abrasive and alcohol wipe was used to prepare the skin. Single-use disposable electrodes were placed on the right FCR muscle over the motor-point. The intensity of stimulation that would be required was established at this point. Recording electrodes were then placed on the other target muscles.

The participant's head was then measured and an initial reference mark placed on the scalp 6 cm lateral and 2cm anterior to the vertex. The 'hotspot' was subsequently determined as the spot on the head that gave the consistently

largest response in the right FCR muscle. Resting motor threshold was determined using the procedures outlined above and a recruitment curve was obtained. This initial recruitment curve was then checked to ensure that threshold had been correctly identified. In the event that the average MEP at threshold was below 50 μ v or above 100 μ v the intensity of simulation was adjusted and a new recruitment curve obtained.

In the experimental session the participant was then moved onto the exercise bike and cycled at the pre-determined intensity for 30 minutes. Two of the female participants found the intensity to be unsustainable and it was adjusted accordingly to ensure that the 30 minutes exercise would be completed. In the control session the participant sat quietly for thirty minutes. At the end of the 30-minute period another recruitment curve was obtained. This was followed by the PAS intervention. To assess the duration of any induced effect, additional recruitment curves were obtained following cessation of the PAS: immediately after, and at 10, 20 and 30 minutes post-intervention. The order in which the participants undertook the experimental and control sessions was counterbalanced.

Genotyping

At the end of the final session (whether experimental or control) a sample of saliva was taken. This was collected using the Oragene collection kit (DNA Genotek, Ottawa, Ontario, Canada), by asking the participant to spit into a vial. When sufficient saliva had been obtained the kit was closed, which mixed the oragene solution with the saliva thus preserving it. DNA will be extracted from these kits using the PCR method and tested to assess which alleles of the BDNF gene each participant carries. Once extracted the DNA may be reanalysed in the future for other markers should they be deemed scientifically relevant.

Results

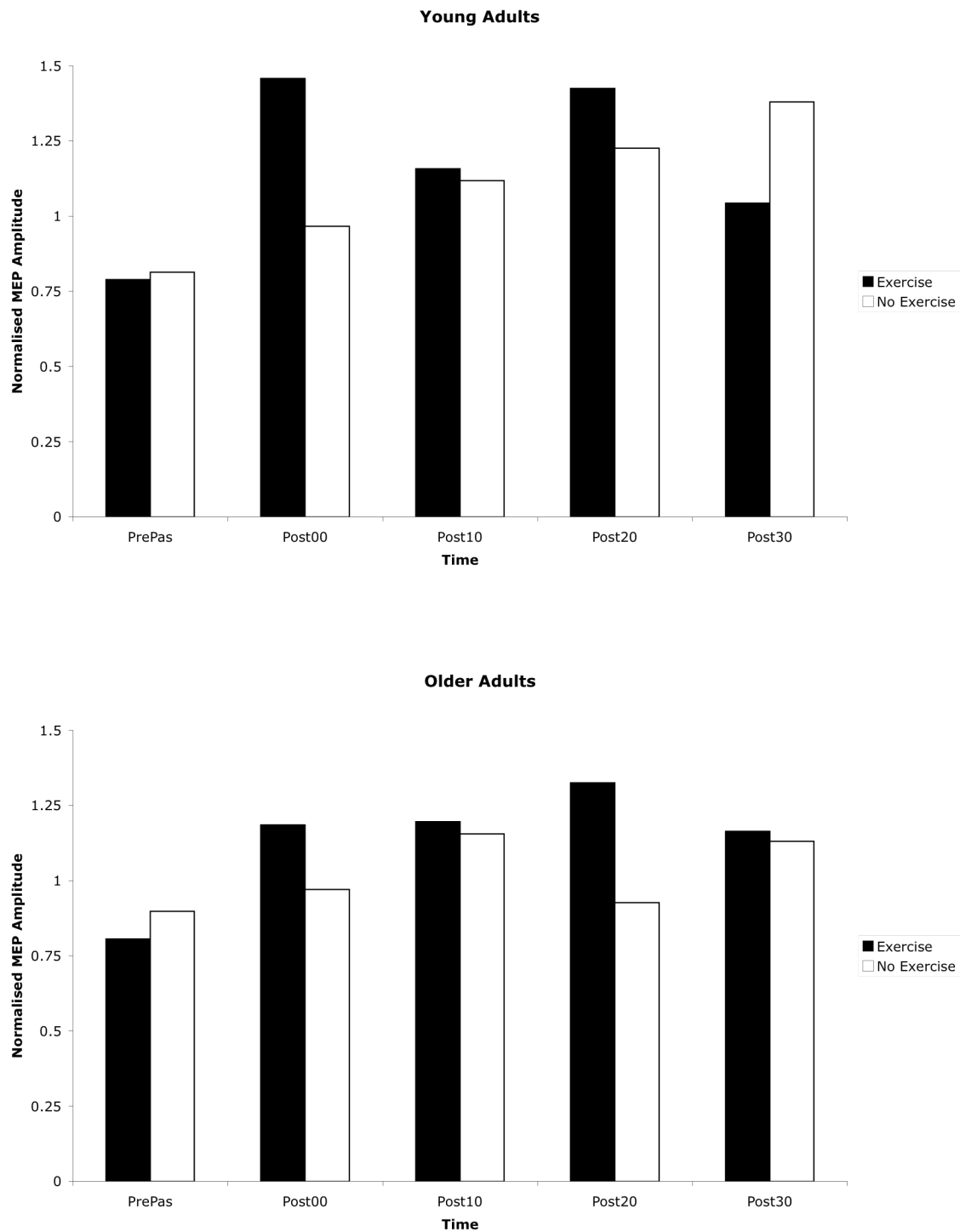


Figure 1: Normalised measures of corticospinal excitability obtained in each of the two conditions (Exercise; No Exercise) prior to (PrePas) and at four time points following the intervention.

Summary of Results

Planned comparisons of means based on an ANOVA design, revealed that in both the exercise and control sessions, the PAS protocol gave rise to reliable increases in corticospinal excitability ($p < 0.03$). These results are in accordance with our previous findings. Notably, both the young and older participants exhibited a similar pattern of change in response to the intervention. It did not appear to be the case that the prior exercise protocol had a reliable impact on the magnitude of these effects. The present findings, while preliminary, suggest that the a preceding bout of moderate intensity aerobic exercise may not impact upon metaplasticity, at least in relation to interventions that alter the excitability of corticospinal projections to muscles in the forearm.

Appendix 1

Telephone Questionnaire

READ: I am going to ask you about the time you spent being physically active in the last 7 days. Please answer each question even if you do not consider yourself to be an active person. Think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Q1

Think about the time you spent walking in the last 7 days. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

Q2

Now think about activities which take *moderate physical effort* that you did in the last 7 days. Moderate physical activities make you breathe somewhat harder than normal and may include carrying light loads, bicycling at a regular pace, or doubles tennis. Do not include walking. Again, think about only those physical activities that you did for at least 10 minutes at a time.

Q3

Now, think about all the *vigorous* activities which take *hard physical effort* that you did in the last 7 days. Vigorous activities make you breathe much harder than normal and may include heavy lifting, digging, aerobics, or fast bicycling. Think only about those physical activities that you did for at least 10 minutes at a time.

Q4

Now think about the time you spent sitting on week days during the last 7 days. Include time spent at work, at home, while doing course work, and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television.

Q1

During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

- Days per week
 Don't Know/Not Sure
 Refused

How much time did you usually spend **walking** on one of those days?

- Hours per day
 Minutes per day

Q2

During the **last 7 days**, on how many days did you do **moderate physical activities**?

- Days per week
 Don't Know/Not Sure
 Refused

How much time did you usually spend doing **moderate physical activities**?

- Hours per day
 Minutes per day

Type of exercise: _____

Q3

During the **last 7 days**, on how many days did you do **vigorous physical activities**?

- Days per week
 Don't Know/Not Sure
 Refused

How much time did you usually spend doing **vigorous physical activities**?

- Hours per day
 Minutes per day

Type of exercise: _____

Q4

During the **last 7 days**, on how much time did you spend **sitting** on a **week day**?

- Hours Per Day
 Don't Know/Not Sure
 Refused

Any other relevant information: