Systematic Review Protocol

Review question

What evidence is there that brain structure is related to muscle structure or function or that muscle structure is related to brain function in humans?

Authors

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Background

As the population of the world ages, studies investigating why humans display different rates of ageing are increasingly important.[1-3] The common cause hypothesis postulates that there are core common underlying processes which drive ageing throughout the human body. The construct was originally used in a paper by Lindenberger and Baltes in 1994 who noted that measures of visual and auditory acuity accounted for variance in intelligence in old age.[4] Since then experiments in caloric restriction have demonstrated that the ageing process can be slowed down in multiple systems throughout the body by one intervention.[5, 6] This finding added weight to the common cause hypothesis.

If the common cause hypothesis is correct there should be a correlation between the structure and function of different organs throughout our lifetime, in the absence of significant pathology. This systematic review will search for evidence to support the hypothesis that brain structure is related to muscle structure and/or function and that muscle structure is related to brain function. We believe no review of this sort has taken place before. Previous studies and reviews have looked at evidence relating brain function (eg MMSE score) to muscle function (eg walking speed) therefore we will not be reviewing this separate but closely related field of literature.[7-10]

Inclusion criteria

Population

All human subjects regardless of age will be included in the study; from newborn babies to the oldest old, including post-mortem studies. This study is examining the effects of ageing on brain and muscle, not the effects of pathology therefore studies looking at how a disease affects brain or muscle will be

excluded. However if a study included a normal control group and the data from these subjects can be extracted separately then this data could be used. As comorbidity (eg Type 2 diabetes) increases in frequency with age it would be impossible to find studies which include elderly subjects with no comorbidity therefore these studies will be included provided the subjects have been recruited in a way that did not pre-dispose to comorbidity being more prevalent than in the general population (eg from a COPD clinic).

Subgroup analysis will be interesting and if possible will include data being extracted to investigate the effects of gender, age, socioeconomic status, ethnicity and geographical area.

Interventions/Comparators

Not applicable as the study is investigating normal physiology.

Outcomes

Brain structure

- Whole brain volume
- Volume or cross sectional area of areas within the brain (eg hippocampus, frontal lobes)
- White matter integrity
- Histological findings about brain structure on autopsy

Brain function

- Any recognised measure of cognitive function including: memory, attention, executive function, language and processing speed
- Reaction time will not be used as this is dependent on aspects of brain and muscle structure and function

Muscle structure

- Muscle cross sectional area on CT, MRI or USS
- Muscle volume (using CT or MRI)
- Whole body lean tissue mass (using DEXA)
- Bioimpedence analysis
- Histological findings on muscle biopsy or on autopsy

Muscle function

- Any recognised test of muscle strength, including isometric, isotonic, isokinetic tests
- Any recognised test of muscle power
- Functional tests of muscle function (eg walking speed, timed get up and go test) with the caveat that these tests do not purely test muscle function alone (eg pain may also play a role)

Study Design

As this review is studying a physiological relationship, intervention studies can not be included unless they contain either a control arm with extractable data with no placebo treatment or baseline data prior to the intervention. Observational studies including cohort studies and cross sectional studies will be used. The control arm of case control studies can also be used. Case reports will be excluded where possible as these would not contain evidence of normal physiological relationships out with pathology. The only other limiter to be used will be "human" in Medline, Embase and PsychInfo but not Cinahl as it appears to screen out human studies erroneously.

Identifying research evidence

We will undertake database searches of Medline, Embase, CINAHL and PsycINFO. All languages will be included in the search. Attempts will be made to search the grey literature. Hand searching through citations and references of relevant articles will also be undertaken.

The following search terms will be used:

Brain Structure	Brain function	Muscle structure	Muscle function
Brain	Cognition	Muscles	Muscle strength
White matter	Cognitive function	Muscle, skeletal	Muscle power
Cerebal cortex	Intelligence tests	Body composition	Grip strength/hand strength
Frontal lobe	Intelligence	Muscular atrophy	Walking
Temporal lobe	Problem solving	Muscle cross sectional area	Physical performance
Parietal lobe	Memory		Physical fitness
Occipital lobe	Mental processes		
Cerebellum			
Brainstem			
Hippocampus			
Brain volume			

Study selection

The search will be undertaken by a clinical fellow in ageing research and an interested junior doctor. We will independently screen the titles +/- abstracts found using our search strategy for relevance. The selected studies will then have the full text of their article reviewed against the inclusion criteria, and reasons for exclusion at this stage will be recorded. At this point we will check to ensure our short lists are the same. Disagreements will be resolved by consensus or adjudication by a third party (Professor in Geriatric Medicine).

Data extraction

The Clinical Fellow will then begin the data extraction. This will include:

General information

- Date of extraction
- Study title
- Study authors
- The journal the study is printed in or type of publication (eg thesis) and date of publication
- Country of origin and language
- Source of funding

Study characteristics

- Aim/objectives of the study
- Study design
- Study inclusion and exclusion criteria
- Recruitment procedures used (e.g. details of randomisation, blinding)

Participant characteristics

- Age
- Gender
- Ethnicity
- Socio-economic status
- Disease characteristics
- Co-morbidities

Setting

- Where the patients were recruited from and where they underwent the testing (eg GP practice, research centre etc)

Outcome data/results

- Statistical techniques used
- For each pre-specified outcome:
    - Whether reported
    - Definition used in study
    - Measurement tool or method used
    - Unit of measurement (if appropriate)
    - Length of follow-up, number and/or times of follow-up measurements
- Results of study analysis e.g. correlation
- For subgroup analysis the above information on outcome data or results will need to be extracted for each patient subgroup
- If using a control group from a case-control or intervention study, record what the pathology being studied was and the number studied in the case group

- Additional outcomes

Quality assessment

Each study will be critiqued following data extraction. This will include reviewing the power of the study, the methods used (eg techniques for measuring muscle strength), the appropriateness of statistical technique used, the selection criteria used and the generalisability of the data. EQUATOR and STROBE guidelines will be used as benchmarks for quality assessment.

Data synthesis

A narrative synthesis will be completed. It is unlikely that the data will be comparable enough to allow meta-analysis (ie different measures of cognition, different muscle groups studied using different machines). However if there is adequate data we will undertake this.

Sub-group analysis will be undertaken. This may only be in the form of a narrative synthesis for the reasons mentioned in the above paragraph, but if possible will be in the form of a meta-analysis.

We will use Endnote as the reference manager.

Dissemination

We plan to present the systematic review at a conference on ageing and publish it in full in a peer reviewed journal.

References

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7. Angevaren, M., et al., *Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment.* Cochrane Database of Systematic Reviews, 2008(3).
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9. Atkinson, H.H., et al., *Cognitive function, gait speed decline, and comorbidities: the health, aging and body composition study.* J Gerontol A Biol Sci Med Sci, 2007. **62**(8): p. 844-50.
10. Alfaro-Acha, A., et al., *Handgrip strength and cognitive decline in older Mexican American's.* Journals of Gerontology Series a-Biological Sciences and Medical Sciences, 2006. **61**(8): p. 859-865.