Handgrip strength is associated with hippocampal volume and white matter hyperintensities in major depression and healthy controls: a U.K. Biobank study

Running title: Muscular strength and brain health

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Objectives

Emerging evidence suggests that handgrip strength (a proxy for muscular fitness) is associated with better cognitive performance in people with major depressive disorder (MDD). The underlying processes are unclear, although hippocampal volume (HCV) reductions and white matter hyperintensities (WMHs) have been implicated. Therefore, we investigated the associations between maximal handgrip strength and volume of various brain regions and WMHs in MDD and healthy controls (HCs).

Methods

We conducted cross-sectional analysis of handgrip strength and neuroimaging data from the U.K. Biobank. Generalised linear models assessed the relationship between grip strength and grey matter, white matter, total brain volume, left and right hippocampus volume and WMHs in MDD and HCs, controlling for age, gender, education and bodyweight.

Results

The final sample included 527 people with MDD (54.3 years, 37.2% male) and 1764 HCs (56.6 years, 53% male). In MDD, stronger handgrip was significantly associated with increased left (Coefficient±S.E= 109.5±27.4) and right (76.6±30.2) HCV. In HCs, only right HCV related to handgrip strength (44.8±17.9). Interaction analyses found stronger associations between grip strength and HCV in MDD compared to HCs, for both hippocampal regions. Stronger handgrip was associated with reduced WMHs in people with MDD (-839.0±277.6) and HCs (-394.1±175.5). Maximal handgrip strength was not associated with grey matter, white matter or total brain volumes in either group.

Conclusions

Stronger grip strength is associated with greater left and right HCV and reduced WMHs in MDD. Future research should investigate directionality and consider if interventions targeting strength/muscular fitness can improve brain health and reduce the neurocognitive abnormalities associated with MDD.

Keywords: mood disorders; exercise; fitness, brain, cognition; hippocampus

Abbreviations: BIANCA, Brain Intensity Abnormality Classification Algorithm; HCs, Healthy Controls; HCV, hippocampal volume; MDD, major depressive disorder; NHS, National Health Service; PHQ, Patient Health Questionnaire; SCID-1, Structured Clinical Interview for DSM-IV Axis I Disorders; U.K., United Kingdom; WHMs, white matter hyperintensities.

Introduction

Globally, major depressive disorder (MDD) is a leading cause of disability (1) and is associated with profound economic burden on health and social care systems(2). In addition to the marked impact on mental health, quality of life and employability(2) people with MDD are at increased risk of a number of physical comorbidities(3) and premature mortality(4). Furthermore, there is increasing recognition that people with MDD also experience deficits in multiple cognitive domains such as executive functioning, memory and attentional processing(5). The deficits in cognitive capacity and function can negatively impact functioning and are burdensome to individuals(6). As such, furthering understanding around the potential mechanisms for the cognitive deficits, such as changes in brain structure and function, is of high priority.

One of the brain regions that have been implicated in MDD onset and for the cognitive deficits experienced is the hippocampus (7). A recent meta-analysis investigating subcortical structures including 1728 MDD patients and 7199 healthy controls identified that reduced hippocampal grey matter volume reductions was evident in MDD, but it did not find any consistent data regarding any other brain regions(8). A further subject of interest is white matter hyperintensities, which are lesions located in the deep white matter, typically sparing subcortical U-fibres, and are often seen together with vessels affected by small vessel disease(9). Specifically, white matter hyperintensities are considered an important marker of ageing related cognition decline, and there is a pressing need to identify potentially modifiable risk factors as targets for therapeutic interventions(10). Indeed, a previous meta-analysis in the general population(9) found that white matter hyperintensities have been associated with an increased

risk of future stroke, cognitive decline, dementia, and premature death, with some evidence that such lesions are notably associated with a faster decline in global cognitive performance, executive function, and processing speed(9). Furthermore, recent evidence has suggested that people with MDD may have increased white matter hyperintensities, and this may be associated with both symptom severity and treatment response(11).

In the general population, there is robust evidence that physical activity and fitness is favorably associated with hippocampal volume(12) and lower degrees of white matter hyperintensities(13). However, the relationship between physical fitness parameters and brain health in psychiatric populations is sparse(14). There is growing interest in the potential for objective physical fitness parameters such as maximal handgrip strength, which provides a simple and valid proxy of overall muscular strength and is recognized as the most suitable measure of muscular function for clinical settings (15, 16). Indeed, weak maximal handgrip strength has been shown to predict incident depression, cardio-metabolic health, and mortality risk in the general population(17).

Furthermore, handgrip strength is emerging as a marker of brain health and cognitive decline, with some evidence showing that it is associated with white matter volume greater hippocampal volume and potentially inversely associated with white matter hyperintensities(18). Due to the rapidly increasing evidence in this area, grip strength can be considered an easily-administered and clinically useful proxy of cognitive function across the lifespan(19). Despite this, the association between handgrip strength and neurocognitive functioning in psychiatric populations is relatively underexplored, although recent large scale studies have demonstrated strong

associations between maximal handgrip strength and cognitive performance across multiple domains in both individuals with schizophrenia(20) bipolar disorder(21), and major depression(21). However, to the best of our knowledge, no previous study has considered if handgrip strength is associated with neurological markers of cognitive decline, such as reduced hippocampal volume and white matter hyperintensities in people with MDD and how this compares to the relationship between handgrip strength and neurological markers found in the general population.

The primary aim of this study is to use population-scale data from the U.K. Biobank to establish how maximal handgrip (a simple proxy for muscular strength) was associated with hippocampal volume (left and right) and white matter hyperintensities in people with MDD and healthy controls. These were selected based on their indicated relationships with physical fitness and/or muscular strength in previous studies of older-age samples(12, 22). A secondary aim was to investigate the association between handgrip strength and the more general brain measures of total brain volume, total grey matter, total white matter that are less specifically related to neurological markers of cognitive decline. On the basis of the existing literature, we hypothesized that greater muscular strength would be associated with larger hippocampal volume and reduced white matter hyperintensities in people with MDD and healthy controls.

Materials and Methods

This study used imaging and grip strength data from the 2nd release of the U.K. Biobank study, containing data from around 10,000 participants. This data was collected between 2014 and 2016 on a single visit to the U.K. Biobank testing centre in Stockport, U.K. Full details of the U.K. Biobank data, including data collection procedures, have been described in detail elsewhere(23). Briefly, the U.K. Biobank is a nationwide, cohort study conducted across 22 dedicated assessment centers throughout the U.K. which sought to understand the relationship between lifestyle, environmental and genetic factors which are associated with various health outcomes(23). Participants were recruited via mail invitations, which were initially sent to approximately 9.2 million U.K. registered addresses. In response to this, a total of 502,664 participants, aged between 37-73 were recruited and data was collected at one of the 22 regional U.K. Biobank assessment centers. Informed consent was obtained from participants before each person undertook an extensive standardized assessment process which included touchscreen questionnaires, in-person interviews, and physical health examinations and tests(23). The U.K. Biobank received NHS ethical approval (Ref. 11/NW/0382) and access to the data and the specific analyses in this study were approved by the U.K. Biobank team (Application Number 22125).

Definition of major depression and healthy controls

In order to define cases of major depression (MDD), we followed previous published and validated criteria.(24) Specifically, case criteria of MDD was determined on the basis of individuals' answers to the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-1) and Patient Health Questionnaire (PHQ)(24) (administered during the baseline visit to the U.K.

Biobank between 2007 – 2010). This information was used to categorize participants as having a single episode of major depression, recurrent major depression (moderate) or recurrent major depression (severe). Categorization of participants with MDD was subsequently validated against other demographic and clinical information available from the U.K. Biobank and lifetime prevalence rates were consistent with other population-based estimates for each disorder across both genders(24). For the purposes of this study, all individuals from the recurrent major depression (moderate or severe) were used for the MDD sample(24). We also identified further individuals with a previous/current ICD-10 diagnosis of recurrent major depression (moderate or severe) using links with hospital diagnostic records.

Healthy controls were defined as people who had completed the mental health questionnaires at the U.K. Biobank baseline visit and given no indication of present or previous affective disorders. We also excluded participants with neurological conditions known to affect cognitive functioning (see Supplement 1) and other severe mental illnesses (schizophrenia and bipolar disorders).

Magnetic Resonance Imaging data

Details of the MRI scan use for the U.K. Biobank have been described in detail elsewhere(25). Briefly, for participants with MDD (n=527) and healthy controls (n=1674) we used measures of subcortical and white matter volumes (all as cubic millimetres, mm^3) acquired using the established U.K. Biobank protocols for this population-scale study. All imaging data was collected using Siemens Skyra 3T scanners (https://www.healthcare.siemens.com/magnetic-resonance-imaging). Preprocessing was undertaken using FSL packages. For T1-weighted data,

segmentation of brain was conducted in two steps: firstly, a tissue-type segmentation using FAST (FMRIB's Automated Segmentation Tool) was applied to grey matter and white matter; then subcortical structures are extracted using FIRST (FMRIB's Integrated Registration and Segmentation Tool). The total white matter and grey matter variables were automatically segmented using FAST normalised for skull size based on the T1 MR scan. This process is fully detailed in the open-access U.K. Biobank MRI protocol, pp.11; https://biobank.ctsu.ox.ac.uk/crystal/docs/brain_mri.pdf). Total volumes (as mm^3) of white matter hyperintensities were calculated based on T1 and T2 FLAIR , derived by the U.K. Biobank team, using the Brain Intensity Abnormality Classification Algorithm (BIANCA) (Griffanti et al., 2016).

Handgrip strength measurement

Participants' handgrip strength was measured by a trained research assistant using a Jamar J00105 hydraulic hand dynamometer following standardized procedures. Briefly, testing began by allowing participants to firstly select the most comfortable of five possible grip positions (ranging between 1.375 - 3.375 inches) for the dynamometer. Participants were than advised to sit upright, keeping their elbow adjacent to their torso, and forearm positioned on an armrest with the thumb was facing upwards. A maximal score was obtained from each person's left and right hand. For the current study, we used the score from a single attempt from participants' self-reported dominant hand. If this was not recorded, we used the hand grip test with the highest value in line with previous U.K. Biobank studies (20, 21).

Confounding variables

Age, gender, education and bodyweight were identified as the key confounding variables. Age, gender and education information were collected from computerized questionnaires completed at U.K. Biobank assessment centers. Highest education/qualifications responses were dichotomized to categorize participants as either having or not having university/college degree-level qualifications. Bodyweight measurement was acquired by a research assistant on-site during the physical health assessments.

Statistical analysis

We aimed to assess factors related to total brain volume, white matter, grey matter, left hippocampal volume, right hippocampal volume and white matter hyperintensities by setting each of these measures as the dependent variable in separate models within the same analytical framework. Linear models (LMs) were run for all brain areas except white matter hyperintensities, where Generalised Linear Model (GLMs) with quasi-Poisson error structure was used (as this measure is essentially count data). For each brain measure, we ran the same structure but separate models for people with MDD and healthy control group. Within each of the models, we primarily aimed to determine the relationship between grip strength (as a continuous measure) and the response variable (brain measure) whilst controlling for factors which are likely to influence the cognitive measure and for which sufficient data were available. Therefore, we fit grip strength, which was scaled and standardized, as a fixed effect along with age, gender, bodyweight (again scaled and standardized) and educational status(20, 21). For each of the models run, we reported appropriate summary statistics regarding the sample

composition (sample size, averages and error surrounding measurements of interest), the model parameter estimates, and associated confidence.

After running these independent models for people with MDD and the healthy control group separately, we then ran the same structure models again but on a combined dataset that included people with MDD and the healthy control group in the same analysis. In these models, we also fitted their sample origin (MDD or control group) as a fixed effect, along with the interaction of this with grip strength. In this way, for each of the brain response variables, we were able to examine whether the relationship with grip strength differed between the two sample groups (MDD or control group).

Finally, as a supplementary analysis, we also carried out each of the primary independent models (for people with MDD and the healthy control group) for each of the separate brain response variables but included an interaction effect between grip strength and age. This was to assess whether there was any support for an age-related change in the relationship between grip strength and each of the brain variables in each of the sample groups.

Results

Included participants

Full details of the participants in the current study are summarized in table 1. The final sample included 1764 healthy controls, with a mean age of 56.7 years, just over half were males (n=935, 53.0%) with a mean weight of 76.9 kilograms (kgs). The 527 MDD participants were of similar age (54.3 years) and weight (77.6 kgs), although there was a higher proportion of females (n=196, 37.2%). The mean maximal grip strength scores were broadly similar in people with MDD (30.5) compared to healthy controls (32.7). Regarding each of the subsequent brain scans, a full data set was available for the 1764 healthy controls and 527 people with MDD for grey matter, white matter, total brain volume, left hippocampus and right hippocampus. A slightly reduced number of 1686 and 494 healthy controls and people with MDD respectively had full data for white matter hyperintensities.

Insert table 1 here

Relationships between grip strength and brain regions

A summary of the (G)LMs examining associations between grip strength and each brain region in people with MDD and healthy controls is presented in Table 2 (with full model output in Supplement 1b). As shown in Figure 1 we found evidence that stronger maximal grip strength was positively associated with greater left (coefficient=108.06±27.6, $p<0.001$ – Figure 1A) and right hippocampal volumes (coefficient=76.8±30.4, $p=0.012$ – Figure 1B) in people with MDD. In the healthy control group, stronger hand grip was associated with increased right

(coefficient=44.7±18.1, p=0.013 – Figure 1D) but not left hippocampal volume (see Figure 1C). Furthermore, the interaction analysis which separately assessed how each of the hippocampal variables was affected by the interaction between grip strength and sample origin (i.e. MDD or healthy control), showed that the relationship between hippocampal volume and grip strength was stronger for people with MDD than for the healthy controls, and this interaction effect was statistically significant in both models (hippocampal left interaction effect: coefficient=70.9±22.5, t=3.15, p=0.002; hippocampal right interaction effect: coefficient=48.6±24.5, t=1.98, p=0.048 – See Supplement 2 for details).

As shown in Figure 2, stronger grip strength was also significantly associated with less white matter hyperintensities in people with MDD (Figure 2A - coefficient=-0.242±0.074, p=0.001) and healthy controls (Figure 2B -coefficient=-0.11±0.044, p=0.014). The interaction analysis found no evidence that this relationship (between grip strength and white matter hyperintensities) was different between people with MDD and the healthy controls (interaction effect: coefficient=-0.078±0.065, z=-1.20, p=0.230 – See Supplement 2 for details).

Insert Table 2 here

There was no evidence of a relationship between maximal handgrip strength in people with MDD and total grey matter (coefficient=1124.8±2556.94, p=0.66), total white matter (coefficient=962.08±2595.09, p=0.711) or total brain volume (coefficient=2086.74±4264.36, p=0.625). Similarly, no relationship was observed in the healthy control group with total grey matter, total white matter or total brain volume (see Table 2). Somewhat expectedly (given these findings), there was also no evidence of an interaction effect between sample origin (people with

MDD or the healthy control group) and grip strength on any of these variables (total grey matter, total white matter, or total brain volume – See Supplement 2 for details). Furthermore, supplementary analysis which reran the primary analysis but assessed whether there was any evidence of an age-related change in the relationship between grip strength and each of the brain variables found no support for an interaction between age and grip strength on any of the focal brain variables in either of the samples i.e. people with MDD or people from the healthy control group (all t/z values <2.0, all p values>0.05).

Discussion

We show that muscular strength is related to structural integrity of key brain regions implicated in the disease onset and progression in MDD, and that handgrip strength provides a simple but useful measure of this relationship. Specifically, using the population-scale dataset of the U.K. Biobank, we found that greater maximal handgrip strength was associated with greater hippocampal volume and reduced white matter hyperintensities in people with MDD and healthy controls, even after adjusting for potential confounders. These results build upon, and potentially explain, the findings of a recent population-scale analysis showing that greater handgrip strength is associated with better cognitive performance in 22,699 people with MDD across multiple cognitive domains (20). Additionally, we also found brain structure in the general population was significantly associated with muscular strength; with significant associations between stronger handgrip and (i) greater right hippocampal volume, (ii) reduced white matter hyperintensities, across over 1,700 individuals. Of note however, our interaction analyses showed that the

associations between grip strength and hippocampal volume were greater in those with MDD than in healthy controls (Supplement 2).

The importance of these findings is contextualized by the growing research demonstrating that white matter hyperintensities are associated with cognitive decline, dementia, stroke and premature mortality(9, 10), leading to a number of researchers stressing the importance of identifying potential therapeutic targeted interventions. A recent meta-analysis found that white matter hyperintensities may be associated with incident later life depression,(26) with an earlier systematic review suggesting a similar relationship in working age adults(27). Surprisingly, little is known about the impact and correlates of white matter hyperintensities in people with MDD and how this compares to the general population, despite a recent study demonstrating that people with MDD experience increased white matter hyperintensities versus controls(28). Such findings are consistent with the hypothesis that vascular factors may contribute to the pathophysiology of depression especially in late-life. A previous small study (n=14) suggested that greater white matter hyperintensities were associated with worse cognitive performance in people with MDD (29). Another small study with 35 people with MDD found white matter hyperintensities were associated with worse executive function and memory scores, and that these results were not explained by cortisol levels(30). Given the fact that increased white matter hyperintensities(11, 31) are pervasive in people with MDD and associated with worse treatment outcomes, our findings of an easy-to-measure, and potentially modifiable, correlate could be important.

The mechanisms which underpin the relationship between handgrip strength and reduced white matter hyperintensities is unclear, although of considerable interest. One potential mechanism is that frequent utilization of muscles (particularly in the context of resistance training) helps to reduce homocysteine and increases levels of insulin-like growth factor 1 (IGF-1), both of which have been associated with cerebral white matter lesions (32). In addition, since handgrip strength is an indicator of whole-body muscle strength and functional capacities, a reduction in muscular strength may reflect a general reduction in physical activity which has been implicated in increased white matter lesions(13). The results could also be partly attributed to reverse causality, as there is some evidence that greater white matter hyperintensities are associated with decreased functional and muscular performance in aging populations(33). However, perhaps the most compelling evidence supporting a causal relationship between muscular strength and brain structure is provided by experimental studies. Specifically, a recent RCT in 100 individuals with mild cognitive impairment found that resistance training significantly increased grey matter volume and reduced white matter hyperintensities in both the right periventricular and parietal zones(34). Importantly, significant improvements were also observed in multiple cognitive domains following the resistance training; showing that interventions which target muscular strength can improve both the functional and neurological deficits observed in cognitive impaired populations(34). Given our findings, alongside the recent literature demonstrating the muscular strength is a marker for cognitive performance in people with depression, clinicians should consider the use of handgrip strength as a marker of cognitive function and brain health in people with depression, and also consider this as a target for interventions. Specifically, resistance training exercise interventions should be explored as an

avenue to address the cognitive decline and changes in white matter hyperintensities that are common in people with depression. Future research is required to address the potential role of resistance training on white matter hyperintensities in people with depression, especially since aerobic exercise does not appear to improve cognitive function in this population(35).

The findings of the relationship between handgrip strength and hippocampal volume in people with MDD are also of considerable interest, since decreased hippocampal volumes have been associated with MDD onset, deterioration and treatment response(11, 31). To the best of our knowledge, consideration of this topic in people with MDD or population cohort studies in the general population remains largely unexplored. Specifically, emerging evidence base suggests that strength training may improve hippocampal volume in the general population(36) possibly through stimulating brain derived neurotrophic factor (BDNF). However, emerging evidence suggests that aerobic and not resistance exercise training increases BDNF(37). Other potential mechanisms of relevance include pro-inflammatory cytokines (e.g. TNF-alpha and IL-6); the role of glucocorticoids and their intracellular amplifier 11beta-hydroxysteroid dehydrogenase type 1, although such mechanisms have not been explored in detail in people with MDD (18). Clearly future research is required to better understand the role of resistance training on hippocampal volume in people with depression. Additionally, given the results of the interaction analysis, future research should aim to determine the extent to which neurocognitive deficits observed in MDD are mediated by physical health status, particularly with regards to muscular functioning.

The specificity of the relationship between handgrip strength and white matter hyperintensities and hippocampal volume is strengthened by the null associations between handgrip strength

with total white, grey and whole brain volume in people with MDD and healthy controls. This suggests that the positive relationships of handgrip strength with reduced white matter hyperintensities and hippocampal regions is more specific than an overall association with volumetric increases in brain size. However, a previous systematic review in the general older adults population found that there was no association between muscle size/function and grey matter volume (three studies), although there was some tentative evidence that muscle size may be related to positive white matter volume (one study) and whole brain volume (2/3 studies finding a positive association) (18).

Whilst the current study builds on earlier work showing that handgrip strength is associated with cognitive performance in people with MDD, suggesting that handgrip strength may serve as a marker of brain health, some limitations should be noted. The cross-sectional design of this study means that further longitudinal and mechanistic research must be conducted to determine the directionality of the relationship between handgrip strength and brain health in people with MDD and the general population. Second, we did not include data on social or occupational functioning which may influence the relationships observed. Third, the mean age of our sample was 55 years, and whilst we control for age in the primary analysis (and also found no evidence of an age-related change in the relationship between grip strength and brain health in supplementary analysis), the results may not generalize to younger populations or those with aging-related neurodegenerative diseases. Fourth, both handgrip strength(38) and the key brain regions studied(39) are associated with multiple genetic loci which may cause these traits to covary, but we did not consider the extent to which genetic heritability contributed to the relationships we

observed. Finally, it should be noted that the Brain Intensity Abnormality Classification Algorithm (BIANCA) used to determine WMHs is still in the beta phase.

Pending confirmatory studies of the directionality of the relationships observed, a next step should be research to consider is if resistance exercise can be a valuable therapeutic intervention to improve cognition for people with MDD. To date, it appears that although aerobic exercise significantly improves cognition in other psychiatric populations, such as schizophrenia (40), there is currently no strong evidence that it confers significant cognitive benefits in people with depression (35). Therefore, resistance training could present a novel and promising intervention for targeting cognitive deficits in this population, as there is increasing evidence from RCTs in older adult people that resistance training promotes neuroplasticity and is associated with consequent improvements in subsequent cognitive function(41). However, the field is current in its infancy and the neurobiological mechanisms underpinning the action of exercise in mood disorders are yet to be elucidated(14).

Figure Legends

Figure 1A-B) The relationship between grip strength with left (top – A & C) and right (bottom – B & D) hippocampal volume in those people with major depression (left – A & B) and healthy controls (right - C & D). Y axis denotes the brain measure considered. Solid red lines show the fit of the models and the red shaded area around these lines shows the associated standard error around this fit. The large blue shaded area shows the range of the raw data measure split into bins of 5% along the raw data. This shows how stronger maximal grip strength was positively associated with greater left hippocampal volumes (1A - 108.06±27.6, $p<0.001$) and right hippocampal volumes (1B - coefficient=76.8±30.4, $p=0.012$) in people with MDD. Further, although stronger hand grip was not significantly associated with left hippocampal volume in the health control group (1C) it was significantly associated with increased right hippocampal volume (1D - coefficient=44.7±18.1, $p=0.013$).

Figure 2A-B) The relationship between grip strength with white matter hyperintensities in (A) major depression and (B) healthy controls. Solid red lines show the fit of the models and the red shaded area around these lines shows the associated standard error around this fit. The large blue shaded area shows the range of the raw data measure split into bins of 5% along the raw data. Stronger grip strength was significantly associated with less white matter hyperintensities in people with MDD (coefficient=-0.242±0.074, $p=0.001$) and healthy controls (coefficient=-0.11±0.044, $p=0.014$).

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Data sharing

The current study uses data from the UK Biobank study using data available for researchers on request from the UK Biobank team. The project number to undertake this research is Application Number 22125. Interested parties in the data should contact the UK Biobank to acquire the data.

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