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ORIGINAL ARTICLE

An integrated brain–behavior model for working memory

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Working memory (WM) is a central construct in cognitive neuroscience because it comprises mechanisms of active information maintenance and cognitive control that underpin most complex cognitive behavior. Individual variation in WM has been associated with multiple behavioral and health features including demographic characteristics, cognitive and physical traits and lifestyle choices. In this context, we used sparse canonical correlation analyses (sCCAs) to determine the covariation between brain imaging metrics of WM-network activation and connectivity and nonimaging measures relating to sensorimotor processing, affective and nonaffective cognition, mental health and personality, physical health and lifestyle choices derived from 823 healthy participants derived from the Human Connectome Project. We conducted sCCAs at two levels: a global level, testing the overall association between the entire imaging and behavioral–health data sets; and a modular level, testing associations between subsets of the two data sets. The behavioral–health and neuroimaging data sets showed significant interdependency. Variables with positive correlation to the neuroimaging variate represented higher physical endurance and fluid intelligence as well as better function in multiple higher-order cognitive domains. Negatively correlated variables represented indicators of suboptimal cardiovascular and metabolic control and lifestyle choices such as alcohol and nicotine use. These results underscore the importance of accounting for behavioral–health factors in neuroimaging studies of WM and provide a neuroscience-informed framework for personalized and public health interventions to promote and maintain the integrity of the WM network.

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INTRODUCTION

Working memory (WM) is the ability to store, update and manipulate goal-relevant information.^{1,2} WM operations engage multiple brain regions but they critically depend on the coordinated activity of a dorsal cortical network anchored in the dorsolateral prefrontal cortex (dlPFC), the parietal cortex (PAR) and the dorsal anterior cingulate cortex (dACC).^{3–5} Within this network, there is evidence of relative functional specialization according to process; the dlPFC is hypothesized to be involved in encoding, setting attentional priorities and manipulating information,^{6,7} the PAR in maintaining attentional focus and storing information^{8,9} and the dACC in error detection and performance adjustment.¹⁰ Regional activation within this network is load dependent and responds to the demand for maintenance, updating and manipulation.^{4,11–13} In addition to regional activation, the WM network can be characterized by its functional and effective connectivity.^{14,15} Functional connectivity represents the statistical dependence of regional changes in blood oxygen level-dependent signal,¹⁶ whereas effective connectivity models the influence that WM-network regions exert over each other.¹⁷

The study of WM is central to cognitive neuroscience because it supports other higher-order cognitive abilities (including but not limited to general fluid intelligence, learning, problem solving and decision making),¹⁸ and lower-order mental operations that require cognitive control.¹⁹ Individual variation in WM is influenced by multiple variables including age, level of education, personality traits,^{20–23} lifestyle choices²⁴ and physical health characteristics.^{22,25} In addition, WM deficits are a prominent

feature of neurological²⁶ and psychiatric conditions²⁷ including psychotic, mood and anxiety disorders and neurodevelopmental and neurodegenerative disorders.

The interrelationship between the function of the WM network and its multiple behavioral and health correlates is of key translational importance but has not been adequately addressed because individual studies commonly focus on a limited number of imaging and behavioral variables. This represents a major drawback when making inferences about the nature of case–control differences in psychiatric neuroimaging as patients commonly differ systematically from controls on multiple behavioral variables that are not related to primary disease mechanisms.²⁸

In this context, we sought to quantify brain–behavior relationships with regard to WM using the unique data set of the Human Connectome Project (HCP, www.humanconnectome.org). Smith *et al.*²⁹ have already demonstrated the value of this approach by defining the covariation matrix between behavioral variables and resting-state connectivity measures derived from 461 HCP participants. They found that the strongest correlations between the behavioral traits and the resting-state connectome concerned higher-order cognitive abilities.²⁹ An obvious implication of these findings is that the correlations between brain connectivity and behavior are primarily driven by brain networks that support higher-order cognitive functions. Working memory and its corresponding core brain network represent the logical first candidate because of the known association of WM with multiple higher-order cognitive functions. In order to test this hypothesis,

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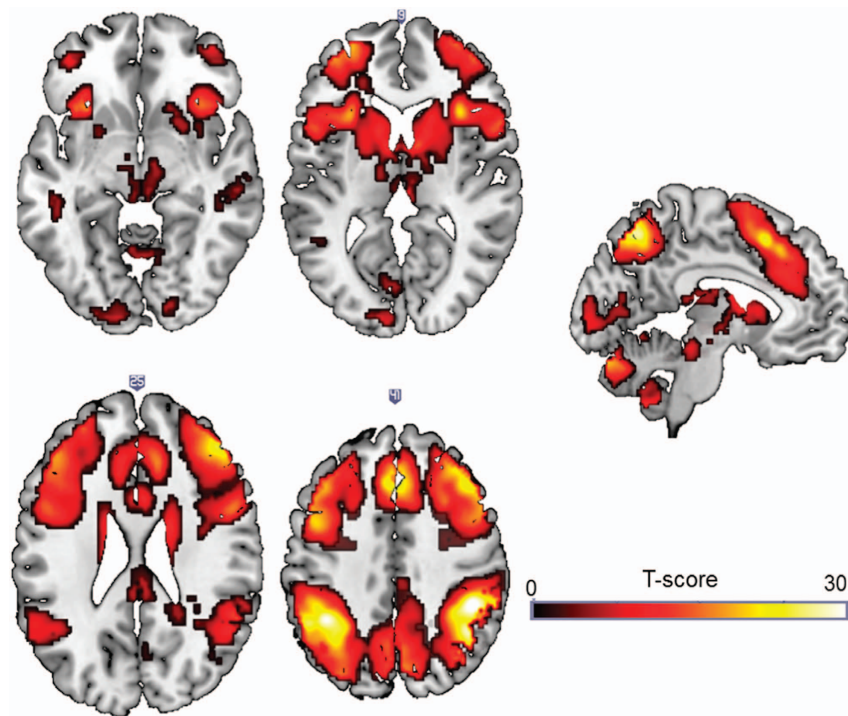


Figure 1. Suprathreshold clusters of activation in the 2-back task. Data derived from the entire sample ($n = 823$); $P < 0.05$ with family-wise error (FWE) voxel-wise correction and minimum $k = 30$ voxels.

we used sparse canonical correlation analyses (sCCAs) to determine the covariation between brain imaging metrics of WM-network activation and connectivity and nonimaging measures relating to sensorimotor processing, affective and non-affective cognition, mental health and personality, physical health and lifestyle choices derived from 823 HCP participants. We refer to these two data sets as the neuroimaging and the ‘behavioral-health’ data sets.

We chose a sparse multivariate approach because it retains brain regional specificity similar to that seen in region of interest analyses³⁰ and it does not require data reduction, regardless of the number of subjects and variables and can be used in smaller samples (more typical in neuroimaging studies). We conducted sCCAs at two levels: a global level, testing the overall association between the entire imaging and behavioral-health data sets; and a modular level, testing associations between modules (that is, subsets) of the two data sets. The purpose of the modular analyses was to facilitate extrapolation of our results to findings available in the literature where similar smaller data sets are the rule. Based on the prior evidence presented above, we hypothesized that imaging and behavioral-health measures will show substantial covariation revealing the interdependent nature of the two data sets; we also hypothesized that correlations would be stronger between neuroimaging and higher-order cognitive function, supporting a key role for the WM-network activation and connectivity.

MATERIALS AND METHODS

Participants

We used data from the HCP database (<http://www.humanconnectome.org>) derived from 823 healthy participants (462 women) with a mean age of 29 years (range 22–37 years). All neuroimaging data were acquired on a Siemens Skyra 3T scanner (Erlanger, Germany) and preprocessed following standard HCP protocols.³¹ All the subjects provided informed consent.³²

This study was approved by the institutional review board of the Icahn School of Medicine at Mount Sinai.

HCP behavior and health measures

We used 116 variables corresponding to demographic characteristics, task performance during sensorimotor processing, affective and nonaffective cognition, mental health and personality, physical health and lifestyle choices (Supplementary Table 1). For variables with both raw and age-adjusted scores, we selected the age-adjusted measures only. We excluded categorical variables ($n = 130$) where $>90\%$ of the sample endorsed the same outcome or that were colinear ($r > 0.9$). For psychometric tests with multiple correlated outcome variables we selected those that are more commonly reported in the literature (see detail in Supplementary Information).

WM-network activation

We analyzed functional magnetic resonance imaging data acquired while participants performed the HCP version of the 2-back task³³ using the Statistical Parametric Mapping software, version 12 (SPM12) (www.fil.ion.ucl.ac.uk/spm/software/spm12/) (details in Supplementary Information). In order to identify WM-related activation, contrast images of the 2-back vs 0-back condition were generated from individual data sets and were then entered into a random-effects group-level one-sample t -test. Suprathreshold clusters were identified at $P < 0.05$ with family-wise error correction at voxel level. As expected based on previous literature,^{3,5} the clusters identified were located bilaterally in the dlPFC, PAR, dACC, the middle temporal gyrus and the visual cortex (VC) (Figure 1). Spherical (radius = 4 mm) volumes of interest (VOIs) were prescribed, centered on the group peak coordinates of each suprathreshold cluster; the radius was chosen to ensure that the VOIs encompassed the individual peak coordinates of all participants. Mean β -values were then extracted and entered in further analyses (Figure 1 and Supplementary Table 2).

Functional connectivity of the WM network

We computed the undirected, model-free functional connectivity of the WM network from the task-based and resting-state data of each

participant. In each data set, we extracted the average time series of the blood oxygen level-dependent signal from the WM-network VOIs described above. Then, we calculated the Fisher's Z-transformed Pearson's correlation between each pair of VOIs to create a resting-state and task-related functional connectivity matrix for each individual.

Effective connectivity

We used dynamic causal modeling (DCM),³⁴ implemented in the DCM12 toolbox to estimate the strength of task-specific modulation (2-back vs 0-back) in the connections between the regions of the WM network. We selected the VOIs in the dlPFC, PAR, dACC and VC, defined as described above based on the results of the second-level analysis (see details in Supplementary Information). This choice was also informed by evidence from meta-analyses^{3,5,35} and previous DCM studies of this WM task.^{17,36} The time series of the homologous VOIs in each hemisphere were averaged to create a 4-region layout of the WM network (Supplementary Figure 2A). The coupling of any two VOIs was defined in terms of intrinsic (task-independent) connections, whereas the impact of the WM condition was modeled directly on the VC (driving input) and on the strength of coupling between each pair of VOIs (modulatory input). In addition, we included a nonmodulated model (null model) as a control. Random-effects Bayesian model selection was used to compute group-level exceedance and posterior probabilities. Finally, to accommodate any uncertainty about the models, we used random effects Bayesian model averaging to obtain average connectivity estimates (weighted by their posterior model probability) across all models and all participants.³⁷

Sparse canonical correlation analyses

A total of 200 imaging and 116 behavioral-health variables were z-standardized and entered into sCCAs implemented using an in-house script³⁰ (see Supplementary Information). We used the same approach for the global and the modular analyses. For each analysis, we computed the sparse parameters by running the sCCA with a range of candidate values (from $0.1 \times \sqrt{p}$ to $1 \times \sqrt{p}$, at 0.1 increments, where p is the number of features in that view of the data) for each imaging and behavioral-health data set and then fitted the resulting models. We selected the optimal sparse criteria combination based on the parameters that corresponded to the values of the model that maximized the sCCA correlation value. We then computed the optimal sCCA model and determined its significance using permutations. Accordingly, the imaging data set was permuted 100 000 times before undergoing the exact same analysis as the original data. The P -value was defined as the number of permutations that resulted in a higher correlation than the original data divided by the total number of permutations. Thus, the P -value is explicitly corrected for multiple testing as it is compared against the null distribution of maximal correlation values across all estimated sCCAs. For each permutation we tested all sparsity criteria combinations as for the original data and then extracted the sCCA correlation with the highest coefficient among the tested options, independently of whether this combination was the same as in the original data. In this way we ensured that we did not underestimate the chance of a permutation achieving the same or higher value than the original data. The threshold for statistical significance for each analysis was set at $P < 0.05$. When the overall sCCA was significant, we investigated the weight of each variable (on both the imaging and behavioral data sets). To do so, we computed Pearson's correlations between each variable and the mode of the opposing pattern (that is, each behavioral-health variable to mode of the neuroimaging data set and vice versa).

Reliability analyses

First, we tested the effect of potential confounders (sex, intracranial volume, acquisition sequence, age) by performing the analysis with and without regressing out these confounds. Second, we confirmed the robustness of the results by randomly resampling half of the sample ($n = 411$) 5000 times and repeating the sCCA each time. Third, we excluded overfitting by using the weights from each of the resampled data and applied them to the other half of the sample. Fourth, we tested whether alternative analyses using CCA would yield the same results. Fifth, to further ensure the robustness of the DCM sCCA results, we tested an alternative DCM model space. Sixth, we tested the specificity of our findings by conducting further analysis examining the association of behavioral-health variables to intrinsic functional connectivity. Seventh,

we conducted further analyses to assess whether our results might be influenced by the fact that some HCP participants are related. For more details on all reliability analyses see Supplementary Information and Supplementary Figures 3 and 4.

RESULTS

The overall design of the study is shown in Supplementary Figure 1. The global analysis considered the covariation of the entire imaging and the entire behavioral-health data set. Modular analyses examined the covariation between distinct subsets (that is, modules) of imaging and behavioral-health data.

Behavioral-health data set

We used 116 variables that were considered as a single data set in the global analysis and as 5 distinct subsets (that is modules) corresponding to psychometric measures of sensorimotor processing, affective and nonaffective cognition, to mental health and personality, and to physical health and lifestyle choices (Supplementary Table 1).

WM-network activation

Conventional general linear analyses of the functional magnetic resonance imaging data identified bilateral clusters located in the dlPFC, dACC, PAR, VC and middle temporal gyrus corresponding to the nodes of the 2-back WM network (Figure 1 and Supplementary Table 2). The resulting variables ($n = 24$) comprised the WM activation module (details in Supplementary Information).

Functional connectivity

We computed the functional connectivity of the WM network based on the results of the second-level analysis described above (and in Supplementary Information). This yielded 66 task-related and 66 resting-state functional connectivity variables comprising the task-related and resting-state functional connectivity module.

Effective connectivity

We used DCM to specify the strength of intrinsic (task-independent) and WM-modulated connectivity of the WM network. The exceedance and the posterior probabilities of the models were computed using random-effects Bayesian model selection. Bayesian model averaging was used to obtain average connectivity estimates across all models for each participant (details in Supplementary Information and Supplementary Figure 2b and c). This analysis generated 44 DCM measures that comprised the effective connectivity module.

Global sparse canonical correlation analysis

The global sCCA quantified the relationship between the two sets of measurements comprising 200 neuroimaging variables and 116 behavioral variables. This analysis showed that the two data sets were significantly associated ($r = 0.50$, $P = 0.00002$) (Figure 2a). Among the behavioral-health variables, those with the highest correlations (positive or negative) with the imaging variate are shown in Figure 2b (and Supplementary Table 3); they included psychometric measures of fluid intelligence, memory, reading/language, visuospatial orientation, sustained attention, mental flexibility and emotional recognition; behavioral traits relating to aggression, physical characteristics relating to physical endurance, body mass index and hemoglobin A1c and lifestyle choices (alcohol use and smoking). Variables with positive correlation to the imaging variate represented positive cognitive and physical attributes, whereas negatively correlated variables represented suboptimal health indicators and lifestyle choices. Among the imaging variables, metrics of activation were more strongly

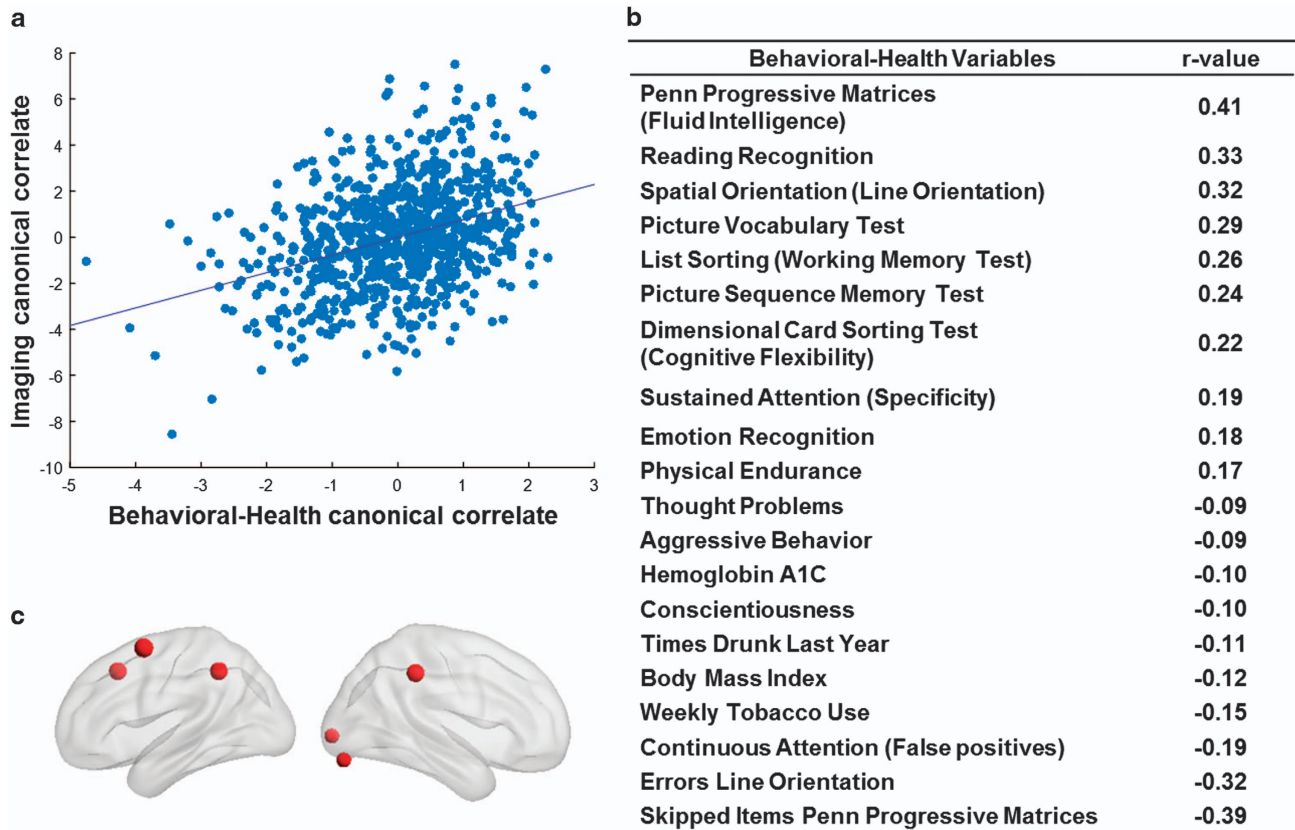


Figure 2. Global sparse canonical correlation analysis. **(a)** Significant correlation between all imaging and behavioral–health variates ($n = 823$, $r = 0.50$, P -value = 0.00002). **(b)** Top behavioral–health variables most strongly associated with the imaging variate. **(c)** Top WM-network activation variables positively associated with the behavioral–health variate. The size of the sphere represents the degree of correlation. WM, working memory.

correlated with the behavioral–health variate (Figure 2c and Supplementary Table 4). Positive correlations were observed with higher activation in the WM network during the 2-back condition and negative correlations with higher WM-network activation during the sensorimotor control condition; greater effective connectivity between the VC to the dlPFC and PAR also showed positive correlations with the behavioral–health variate, whereas the opposite was the case with regard to increased effective connectivity between the dACC and other WM-network regions (Supplementary Table 4).

Modular sparse canonical correlation analyses

At this level, sCCAs were implemented to test the covariation of each neuroimaging module to each of the behavioral modules (Figures 1 and 3; Supplementary Tables 5 and 6 and Supplementary Data Set). The results of these analyses largely recapitulated those of the global sCCA. We found that the WM-task activation variate was significantly associated with affective and nonaffective cognition, mental health and personality, physical health and lifestyle. The behavioral variables that were most strongly associated with the WM-task activation were fluid intelligence, language, memory and abstraction (nonaffective cognition module), facial emotion recognition (affective cognition module), openness (mental health and personality) and physical endurance (physical health and lifestyle). The DCM variate was only associated with the nonaffective cognition module (primarily fluid intelligence, language and spatial orientation). Both task and resting-state functional connectivity variates were primarily associated with the physical health and lifestyle module; positive correlations were observed with better endurance, higher

hematocrit and sleep quality (as measure in the total score of the Pittsburgh Sleep Questionnaire), whereas higher body mass index as well as high blood pressure and poor glucose control had a detrimental effect. The association between physical health measures was not specific to the WM network as it was also observed in connection to whole-brain functional connectivity (details in Supplementary Information).

Reliability analyses

For the global analysis, half of the sample ($n = 411$) was randomly resampled 5000 times. The sCCAs repeated each time resulted in a mean r -value = 0.53 (s.d. = 0.04). We used the weights of each sCCA permutation to the respective 5000 sets of the remaining half of the sample. These scores yielded a mean r -value = 0.39 (s.d. = 0.06). For the modular analyses, no difference above 2 s.d. was found between the averaged resampled data and the actual data, for any of the significant models (Supplementary Table 7), confirming the reliability of the present results. The sCCA results were virtually unchanged regardless of whether we regressed out or stratified the analysis to account for intracranial volume, acquisition sequence, sex and age. We use sex to illustrate this; as shown in Supplementary Information (Supplementary Table 8), no differences were found in the global analysis between the main results and results of separate sCCAs for men ($n = 361$) and women ($n = 462$). Finally, the results remained unchanged when we used alternative definitions of the DCM model space, when we computed regular CCAs instead of sCCAs (Supplementary Table 9) and when accounting for family structure (details for all these analyses in Supplementary Information).

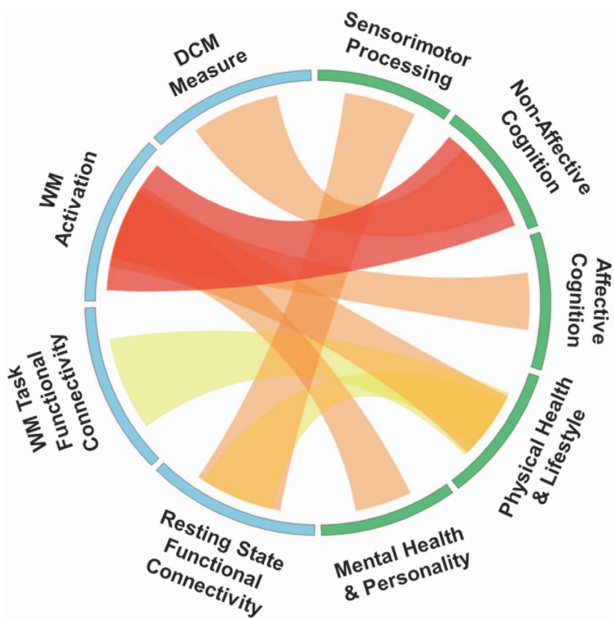


Figure 3. Modular sparse canonical correlation analysis. The connections between the modules are sized based on the r -values. Yellow connections indicate significant associations at $P < 0.05$; orange connections indicate significant associations at $P < 0.01$; red connections indicate significant associations at $P < 0.001$. DCM, dynamic causal modeling; WM, working memory.

DISCUSSION

We used the rich data set of the HCP to quantify brain-behavior covariation relevant to working memory. We found that cognitive measures reflecting better general intellectual ability, visuospatial skills, language, attention and mental flexibility were among the behavioral measures with the strongest positive correlations to imaging phenotypes indexing WM-network function. In contrast, variables relating to aggression, substance use and suboptimal cognition were among the behavioral measures with the strongest negative correlations to imaging phenotypes indexing WM-network function.

Fluid intelligence had the strongest positive correlation with neuroimaging phenotypes of WM function both in the global and modular analyses. This observation significantly enhances our understanding of the relationship between fluid intelligence and WM, a topic that has been debated for nearly three decades.³⁸ We show that even when multiple other variables are taken into account, fluid intelligence remains strongly correlated with WM-network functional integrity. This suggests that both cognitive constructs are supported by common neural mechanisms. The close link between intelligence and WM is further supported by a recent study that examined individual variability in functional brain connectivity;³⁹ the WM-network connectome had the most distinctive fingerprint at the individual level and was the most significant predictor of fluid intelligence.³⁹ Consistent with the notion that the WM-network identified via the 2-back task has a domain-general role,^{18,19} we found that WM-network activation and effective connectivity were associated with a wide range of higher-order functions relating to executive control of attention, visual orientation and language (see also Supplementary Discussion).

The global and modular analyses identified several lifestyle choices and physical traits that showed significant covariation with WM-network imaging metrics. Among lifestyle choices, alcohol binge drinking and regular weekly smoking were negatively correlated with WM-network function. Alcohol-related WM dysfunction across the lifespan has been amply documented

in prior literature^{40,41} and is further supported by the current study. Nicotine enhances attention and cognition, including WM,⁴² in a baseline-dependent manner such that individuals with lower baseline function benefit the most from nicotine use.⁴³ This mechanism has been proposed to explain initiation and maintenance of smoking. It is therefore possible that the negative correlation between weekly smoking levels and WM-network function reflects lower baseline WM-network function in smokers. Alternatively, nicotine abstinence in smokers leads to reduced WM performance compared with nonsmokers⁴⁴ and is associated with lower blood oxygen level-dependent signal in the frontoparietal WM-network regions.⁴⁵ Our results may therefore reflect some aspect of abstinence-related WM-network dysfunction, as access to nicotine is restricted during scanning. Better physical endurance was positively associated with WM-network activation and connectivity. Conversely, suboptimal blood pressure and glucose control and higher body mass index had a negative effect on functional connectivity. This close dependency between physical traits and task-related brain activation, connectivity and resting-state connectivity is not specific to WM as it was also observed in connection to whole-brain resting-state connectivity as shown in our supplementary analyses. The same correlation pattern has also been reported in data from the 5000 participants of the UKBiobank⁴⁶ and is likely to reflect the fact that these imaging metrics are directly derived from changes in the hemodynamic brain responses and seem sensitive to cardiometabolic factors that may affect blood oxygenation. These observations are of potential translational value in view of recent studies^{47,48} showing that increased physical activity could improve WM-related performance and brain phenotypes. In addition, the role of physical traits and lifestyle choices for WM-network function bolsters arguments for accounting for these variables when using neuroimaging to examine clinical populations before making inferences about specific-disease related mechanisms.²⁸

Age made a limited contribution to the results, likely because of the restricted age range of the HCP participants. There was no effect of sex on the sCCA models, in line with previous reports that, unlike other aspects of brain structure and function, the WM-network may not be sexually dimorphic.^{21,49}

Our study has several limitations. The 2-back task does not isolate distinctive components of WM (for example, goal maintenance, storage capacity, interference control). It is therefore possible that the multifactorial nature of the 2-back task may lead to greater overlap with fluid intelligence than might be the case with other paradigms that map onto specific WM component (for example, oculomotor delayed response³⁷ and Sternberg spatial memory tasks⁴⁰ that dissociate encoding and maintenance processes). Neuroimaging techniques include other modalities (such as diffusion weighted imaging and magnetic resonance spectroscopy) and other analytical methods (such as graph theory and dynamic connectivity) that were not considered here. Nevertheless, our study examined those modalities and analytical methods that are most commonly used in neuroimaging studies of WM. Finally, the correlational nature of the analyses does not resolve causality, but the results are still important as they identify modifiable potential risk factors for WM dysfunction.

In conclusion, we describe a brain-behavior model for WM that demonstrates a positive association between WM-network function with variables reflecting better cognitive abilities and physical well-being, whereas the opposite was the case for indicators of suboptimal health and substance use. We confirm that the WM network is closely linked to general intellectual ability and acts as a domain-general network to support multiple higher-order cognitive functions. The dependency of neuroimaging phenotypes on behavioral-health measures suggests that such factors should be considered as potential confounds in clinical studies and as modifiable targets could inform personalized interventions and public health efforts for the promotion of mental well-being.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

- 1 Baddeley A. Working memory: theories, models, and controversies. *Annu Rev Psychol* 2012; **63**: 1–29.
- 2 Diamond A. Executive functions. *Annu Rev Psychol* 2013; **64**: 135–168.
- 3 Fletcher PC, Henson RN. Frontal lobes and human memory: insights from functional neuroimaging. *Brain* 2001; **124**(Pt 5): 849–881.
- 4 Owen AM, Herrod NJ, Menon DK, Clark JC, Downey SP, Carpenter TA et al. Redefining the functional organization of working memory processes within human lateral prefrontal cortex. *Eur J Neurosci* 1999; **11**: 567–574.
- 5 Wager TD, Smith EE. Neuroimaging studies of working memory: a meta-analysis. *Cogn Affect Behav Neurosci* 2003; **3**: 255–274.
- 6 D'Esposito M, Postle BR, Rypma B. Prefrontal cortical contributions to working memory: evidence from event-related fMRI studies. *Exp Brain Res* 2000; **133**: 3–11.
- 7 Narayanan NS, Prabhakaran V, Bunge SA, Christoff K, Fine EM, Gabrieli JD. The role of the prefrontal cortex in the maintenance of verbal working memory: an event-related fMRI analysis. *Neuropsychology* 2005; **19**: 223–232.
- 8 Guerin SA, Miller MB. Parietal cortex tracks the amount of information retrieved even when it is not the basis of a memory decision. *Neuroimage* 2011; **55**: 801–807.
- 9 Jonides J, Schumacher EH, Smith EE, Koeppe RA, Awh E, Reuter-Lorenz PA et al. The role of parietal cortex in verbal working memory. *J Neurosci* 1998; **18**: 5026–5034.
- 10 Carter CS, Botvinick MM, Cohen JD. The contribution of the anterior cingulate cortex to executive processes in cognition. *Rev Neurosci* 1999; **10**: 49–57.
- 11 Braver TS, Cohen JD, Nystrom LE, Jonides J, Smith EE, Noll DC. A parametric study of prefrontal cortex involvement in human working memory. *Neuroimage* 1997; **5**: 49–62.
- 12 Callicott JH, Mattay VS, Bertolino A, Finn K, Coppola R, Frank JA et al. Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. *Cereb Cortex* 1999; **9**: 20–26.
- 13 Volle E, Kinkingnehun S, Pochon JB, Mondon K, Thiebaut de Schotten M, Seassau M et al. The functional architecture of the left posterior and lateral prefrontal cortex in humans. *Cereb Cortex* 2008; **18**: 2460–2469.
- 14 Braun U, Schafer A, Walter H, Erk S, Romanczuk-Seiferth N, Haddad L et al. Dynamic reconfiguration of frontal brain networks during executive cognition in humans. *Proc Natl Acad Sci USA* 2015; **112**: 11678–11683.
- 15 Sala-Llonch R, Pena-Gomez C, Arenaza-Urquijo EM, Vidal-Pineiro D, Bargallo N, Junque C et al. Brain connectivity during resting state and subsequent working memory task predicts behavioural performance. *Cortex* 2012; **48**: 1187–1196.
- 16 Friston KJ. Functional and effective connectivity: a review. *Brain Connect* 2011; **1**: 13–36.
- 17 Dima D, Jogia J, Frangou S. Dynamic causal modeling of load-dependent modulation of effective connectivity within the verbal working memory network. *Hum Brain Mapp* 2014; **35**: 3025–3035.

- 18 Kane MJ, Conway ARA, Hambrick DZ, Engle RW. Variation in working memory capacity as variation in executive attention and control. In: Conway ARA, Jarrold C, Kane MJ, Miyake A, Towse JN(eds) *Variation in Working Memory*. Oxford University Press: New York, 2007, pp 21–48.
- 19 Engle RW, Kane MJ. Executive attention, working memory capacity and two-factor theory of cognitive control. In: Ross B(ed) *The Psychology of Learning and Motivation*. Elsevier: New York, 2004 pp 145–199.
- 20 Dima D, Friston KJ, Stephan KE, Frangou S. Neuroticism and conscientiousness respectively constrain and facilitate short-term plasticity within the working memory neural network. *Hum Brain Mapp* 2015; **36**: 4158–4163.
- 21 Hill AC, Laird AR, Robinson JL. Gender differences in working memory networks: a BrainMap meta-analysis. *Biol Psychol* 2014; **102**: 18–29.
- 22 Rannikko I, Jaaskelainen E, Miettinen J, Ahmed AO, Veijola J, Remes AM et al. Predictors of long-term change in adult cognitive performance: systematic review and data from the Northern Finland Birth Cohort 1966. *Clin Neuropsychol* 2016; **30**: 17–50.
- 23 Wang M, Gamo NJ, Yang Y, Jin LE, Wang XJ, Laubach M et al. Neuronal basis of age-related working memory decline. *Nature* 2011; **476**: 210–213.
- 24 Tempest GD, Davranche K, Brisswalter J, Perrey S, Radel R. The differential effects of prolonged exercise upon executive function and cerebral oxygenation. *Brain Cogn* 2017; **113**: 133–141.
- 25 Gottesman RF, Schneider AL, Albert M, Alonso A, Bandeen-Roche K, Coker L et al. Midlife hypertension and 20-year cognitive change: the atherosclerosis risk in communities neurocognitive study. *JAMA Neurol* 2014; **71**: 1218–1227.
- 26 Matthews BR. Memory dysfunction. *Continuum (Minneapolis)* 2015; **21**(3 Behavioral Neurology and Neuropsychiatry): 613–626.
- 27 Millan MJ, Agid Y, Brune M, Bullmore ET, Carrey CS, Clayton NS et al. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. *Nat Rev Drug Discov* 2012; **11**: 141–168.
- 28 Weinberger DR, Radulescu E. Finding the elusive psychiatric "lesion" with 21st-century neuroanatomy: a note of caution. *Am J Psychiatry* 2016; **173**: 27–33.
- 29 Smith SM, Nichols TE, Vidaurre D, Winkler AM, Behrens TE, Glasser MF et al. A positive-negative mode of population covariation links brain connectivity, demographics and behavior. *Nat Neurosci* 2015; **18**: 1565–1567.
- 30 Witten DM, Tibshirani R, Hastie T. A penalized matrix decomposition, with applications to sparse principal components and canonical correlation analysis. *Biostatistics* 2009; **10**: 515–534.
- 31 Glasser MF, Sotiropoulos SN, Wilson JA, Coalson TS, Fischl B, Andersson JL et al. The minimal preprocessing pipelines for the Human Connectome Project. *Neuroimage* 2013; **80**: 105–124.
- 32 Van Essen DC, Barch DM. The human connectome in health and psychopathology. *World Psychiatry* 2015; **14**: 154–157.
- 33 Barch DM, Burgess GC, Harms MP, Petersen SE, Schlaggar BL, Corbetta M et al. Function in the human connectome: task-fMRI and individual differences in behavior. *Neuroimage* 2013; **80**: 169–189.
- 34 Friston KJ, Harrison L, Penny W. Dynamic causal modelling. *Neuroimage* 2003; **19**: 1273–1302.
- 35 Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Hum Brain Mapp* 2005; **25**: 46–59.
- 36 Dima D, Roberts RE, Frangou S. Connectomic markers of disease expression, genetic risk and resilience in bipolar disorder. *Transl Psychiatry* 2016; **6**: e706.
- 37 Chafee MV, Goldman-Rakic PS. Matching patterns of activity in primate prefrontal area 8a and parietal area 7ip neurons during a spatial working memory task. *J Neurophysiol* 1998; **79**: 2919–2940.
- 38 Kyllonen PC, Christal RE. Reasoning ability is (little more than) working-memory capacity? *Intelligence* 1990; **14**: 389–433.
- 39 Finn ES, Shen X, Scheinost D, Rosenberg MD, Huang J, Chun MM et al. Functional connectome fingerprinting: identifying individuals using patterns of brain connectivity. *Nat Neurosci* 2015; **18**: 1664–1671.
- 40 Mayhugh RE, Moussa MN, Simpson SL, Lyday RG, Burdette JH, Porrino LJ et al. Moderate-heavy alcohol consumption lifestyle in older adults is associated with altered central executive network community structure during cognitive task. *PLoS ONE* 2016; **11**: e0160214.
- 41 Silveri MM, Dager AD, Cohen-Gilbert JE, Sneider JT. Neurobiological signatures associated with alcohol and drug use in the human adolescent brain. *Neurosci Biobehav Rev* 2016; **70**: 244–259.
- 42 Heishman SJ, Kleykamp BA, Singleton EG. Meta-analysis of the acute effects of nicotine and smoking on human performance. *Psychopharmacology (Berl)* 2010; **210**: 453–469.
- 43 Niemegeers P, Dumont GJ, Quisenbaerts C, Morrens M, Boonzaier J, Franssen E et al. The effects of nicotine on cognition are dependent on baseline performance. *Eur Neuropsychopharmacol* 2014; **24**: 1015–1023.
- 44 Grundey J, Amu R, Ambrus GG, Batsikadze G, Paulus W, Nitsche MA. Double dissociation of working memory and attentional processes in smokers and

- non-smokers with and without nicotine. *Psychopharmacology (Berl)* 2015; **232**: 2491–2501.
- 45 McClernon FJ, Froeliger B, Rose JE, Kozink RV, Addicott MA, Sweitzer MM *et al*. The effects of nicotine and non-nicotine smoking factors on working memory and associated brain function. *Addict Biol* 2016; **21**: 954–961.
- 46 Miller KL, Alfaro-Almagro F, Bangerter NK, Thomas DL, Yacoub E, Xu J *et al*. Multimodal population brain imaging in the UK Biobank prospective epidemiological study. *Nat Neurosci* 2016; **19**: 1523–1536.
- 47 Hillman CH, Erickson KI, Kramer AF. Be smart, exercise your heart: exercise effects on brain and cognition. *Nat Rev Neurosci* 2008; **9**: 58–65.
- 48 Felez-Nobrega M, Hillman CH, Cirera E, Puig-Ribera A. The association of context-specific sitting time and physical activity intensity to working memory capacity and academic achievement in young adults. *Eur J Public Health* 2017; **27**: 741–746.

- 49 Schmidt H, Jorgia J, Fast K, Christodoulou T, Haldane M, Kumari V *et al*. No gender differences in brain activation during the N-back task: an fMRI study in healthy individuals. *Hum Brain Mapp* 2009; **30**: 3609–3615.



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