An Open Publishing Platform of the Organization for Human Brain Mapping
APERTURE NEURO

RESEARCH ARTICLE

Body Mass Index Moderates Brain Dynamics and Executive Function: A Structural Equation Modeling Approach

Lauren Kupis,[a] Zachary T. Goodman,[b] Salome Kornfeld,[b] Celia Romero,[b] Bryce Dirks,[b] Leigha Kircher,[b] Catie Chang,[c,d,e] Maria M. Llabre,[b] Jason S. Nomi,[a] Lucina Q. Uddin[a*]

[a] Department of Psychiatry, University of California Los Angeles, Los Angeles, CA, USA
[b] Department of Psychology, University of Miami, Coral Gables, FL, USA
[c] Department of Electrical Engineering and Computer Science, Vanderbilt University, Nashville, TN, USA
[d] Department of Biomedical Engineering, Vanderbilt University, Nashville, TN, USA
[e] Vanderbilt University Institute of Imaging Science, Vanderbilt University, Nashville, TN, USA

ABSTRACT

Obesity is associated with negative physical and mental health outcomes. Being overweight/obese is also associated with executive functioning impairments and structural changes in the brain. However, the impact of body mass index (BMI) on the relationship between brain dynamics and executive function (EF) is unknown. The goal of the study was to assess the modulatory effects of BMI on brain dynamics and EF. A large sample of publicly available neuroimaging and neuropsychological assessment data collected from 253 adults (18–45 years; mean BMI 26.95 kg/m^2 ± 5.90 SD) from the Nathan Kline Institute (NKI) were included (http://fcon_1000.projects.nitrc.org/indi/enhanced/). Participants underwent resting-state functional MRI and completed the Delis–Kaplan Executive Function System (D-KEFS) test battery (1). Time series were extracted from 400 brain nodes and used in a co-activation pattern (CAP) analysis. Dynamic CAP metrics including dwell time (DT), frequency of occurrence, and transitions were computed. Multiple measurement models were compared based on model fit with indicators from the D-KEFS assigned *a priori* (shifting, inhibition, and fluency). Multiple structural equation models were computed with interactions between BMI and the dynamic CAP metrics predicting the three latent factors of shifting, inhibition, and fluency while controlling for age, sex, and head motion. Models were assessed for the main effects of BMI and CAP metrics predicting the latent factors. A three-factor model (shifting, inhibition, and fluency) resulted in the best model fit. Significant interactions were present between BMI and CAP 2 (lateral frontoparietal (L-FPN), medial frontoparietal (M-FPN), and limbic nodes) and CAP 5 (dorsal frontoparietal (D-FPN), midcingulo-insular (M-CIN), somatosensory motor, and visual network nodes) DTs associated with shifting. A higher BMI was associated with a positive relationship between CAP DTs and shifting. Conversely, in average and low BMI participants, a negative relationship was seen between CAP DTs and shifting. Our findings indicate that BMI moderates the relationship between brain dynamics of networks important for cognitive control and shifting, an index of cognitive flexibility. Furthermore, higher BMI is linked with altered brain dynamic patterns associated with shifting.

Keywords: executive function, cognitive control, and decision-making, connectivity
Correspondence: Lauren Kupis, University of California Los Angeles, Los Angeles, CA 90095, Email: lkupis@g.ucla.edu
Received: January 27, 2021
Accepted: August 10, 2021
DOI: 10.52294/8944e106-c54b-40d7-a620-925f7b074f99

INTRODUCTION

Overweight and obesity are prevalent in one-third of the global population (2) and 42.4% of adults in the United States (3). Obesity accounts for over 2.8 million deaths per year (4), and a body mass index (BMI) ≥30 is additionally a risk factor for greater complications as a result of the novel coronavirus (COVID-19) (5). Overweight (BMI 25 to <30) and obesity are typically considered physical health conditions associated with comorbid conditions such as type II diabetes and cardiovascular disease (6). In addition to these health concerns, obesity is increasingly linked with cognitive impairments and brain alterations (7–9). Cognitive impairments are found to worsen with increasing BMI (10,11) throughout the lifespan (11). Additionally, obesity during midlife is associated with greater risks of dementia (12) and brain atrophy in later life (13).

Accumulating evidence supports cognitive impairment in the form of executive function (EF) deficits in overweight/obese individuals (14,15). EFs are higher-order cognitive processes that enable goal-oriented behaviors (16,17) and are important for various aspects of daily functioning including maintaining a job (18), social functioning (19,20), and well-being (21). EFs can be divided into distinct but related components (22) including inhibition, cognitive flexibility, and updating (23,24). A recent meta-analysis revealed that individuals with obesity primarily show impairments on EF tasks that require inhibition, cognitive flexibility, working memory, decision-making, verbal fluency, and planning (15). Additionally, impairments in EF and overweight/obesity are associated with negative impacts on mental health such as anxiety and depression (25–28).

A common neuropsychological test used to assess EF is the Delis–Kaplan Executive Function System (D-KEFS) (1). The D-KEFS consists of nine tests of varying EF components; however, composite scores within the tests have been tested as construct-specific factors rather than stand-alone tests (29,30). The use of latent variables as dependent variables reduces the task impurity problem by tapping into the underlying construct rather than relying on one impure measure of a task. The latent variable is characterized by statistical extraction of the variance shared by multiple tasks that are thought to require the same executive control ability, resulting in a purer measure of the ability (31,32). The D-KEFS does not include direct tests within the latent factor of updating (i.e., continuously monitoring working memory and updating content), which is thought to be one of three EF constructs in well-known latent models of executive functioning (23). The three constructs instead include shifting, inhibition, and fluency (33). The three latent factors of D-KEFS are defined as follows: (1) shifting or the mental ability to switch or shift in response to changing stimuli (an index of cognitive flexibility) (34); (2) inhibition or the ability to control one's behavior and thoughts to inhibit responses (16); and (3) fluency, thought to underlie executive control and updating (35), fluency in generating new designs (i.e., creativity) (36), and an index of verbal abilities.

Recent studies examining brain functional connectivity in overweight/obesity have identified alterations in brain networks rather than specific brain regions that may impact EF. Studies have reported network alterations among the midcingulo-insular/salience network (M-CIN), medial frontoparietal/default network (M-FPN), and lateral frontoparietal/central executive network (L-FPN) in overweight/obese individuals (37–45). The M-CIN plays a role in detecting salient information and coordinating transitions between the L-FPN and M-FPN; the L-FPN is involved in executive or control processes; the M-FPN is involved in self-referential thoughts and monitoring of the environment (46). The dynamic relationships among these three core neurocognitive networks are additionally thought to enable flexible cognition (46,47), important for EFs. Alterations among the M-CIN, L-FPN, and M-FPN in overweight/obesity provide further support for altered reward processing and EF, and cognitive and emotional processing of salient food cues (48). Alterations among these networks have also been previously associated with various neuropsychiatric disorders (49), suggesting these networks are important treatment targets for populations such as obese individuals.

Evidence of brain alterations among the three large-scale neurocognitive networks provides important insights into potential neural mechanisms underlying behavior; however, whole-brain functional connectivity studies have revealed alterations among other regions in overweight/obese individuals. Functional connectivity alterations have been observed between the aforementioned three large-scale networks and visual (39,45,50), limbic (44), sensorimotor (39,51), and dorsal frontoparietal networks (D-FPN; dorsal attention) (39). These findings suggest that it is important to examine whole-brain network relationships in overweight/obesity. Further, brain regions important for monitoring external and internal processes are altered in overweight/obesity (39–45) and suggest that BMI may alter the way network flexibility is associated with flexible behavior such that reduced network flexibility may be linked with poorer EF and adaptive behavior.

There are very few studies to date that have examined the relationship among EF, BMI, and the brain (52–54), and no study to date has examined the relationship among BMI, brain network dynamics, and EF. Brain network dynamics have previously been shown to predict EF performance irrespective of BMI (55). Recent work has also shown that brain network dynamics of the L-FPN, thought to underlie EFs, were correlated with BMI (56). Additionally, increased BMI (overweight/obesity) is associated with reduced cerebral blood flow (57). Neural activity in the brain is dependent on cerebral blood flow (58–60), and cerebral blood flow is correlated with functional connectivity strength (61). Further, brain dynamics represent time-varying brain states (62) that may also be modulated by cerebral blood flow (63). Combined with the previously noted influence of BMI on cerebral blood flow, it is plausible to infer that the relationship between brain dynamics and EF may be moderated by an individual's BMI; however, this has not been previously tested.

Although there is evidence that dynamic brain function is associated with EF performance (55,64,65), brain dynamic patterns are not consistently associated with each EF (e.g., shifting but not inhibition or fluency/updating) (55,64), leading to the question of whether another variable (e.g., moderator) could be accounting for the differences. Further, altered functional connectivity among regions important for EF is accompanied by impaired EF in individuals with a higher BMI, but not in individuals within a healthy BMI (37). This suggests that the relationship between brain function and EF may vary depending on an individual's BMI (e.g., optimal brain function is related to

optimal EF in healthy-weight individuals, but poorer brain function is related to poorer EF in overweight/obese individuals). Together, this implies that BMI may be tested as a moderator of the relationship between brain dynamics and EF as previously done in other fields (66,67) to better understand how the relationship between two variables is affected by varying levels of BMI (68).

In this study, BMI was tested as a moderator primarily due to the following reasons: (1) previous evidence of brain dynamics supporting EF (55,64); (2) the unclear directionality among BMI, EF, and brain dynamics (69,70); (3) previous work examining brain structure and functional connectivity rather than brain dynamics; (4) access to cross-sectional data; (5) previous work using BMI as a moderator; and (6) the use of a population (young to middle-aged adults) where brain function is optimal (71–74) and less is known in this population regarding EF and brain function related to BMI (75,76). By adopting a moderator framework, the relationship between brain function and EF can be examined at different levels of BMI. Such insight may benefit researchers and clinicians when assessing young- to middle-aged adults at varying BMI levels and overweight/obese adults who may be at greater risk of altered time-varying brain function paired with poorer cognition.

Functional connectivity and structural neuroimaging methods have provided insight into brain organization differences in overweight/obese individuals; however, recent developments in neuroimaging posit dynamic methods, such as sliding window correlations (77,78) and co-activation patterns (CAPs) (77,79), may be applied to capture time-varying changes in the brain architecture (see (62)). Further, dynamic or time-varying methods may, in some cases, better capture relationships between brain function and cognition and behavior than static functional connectivity methods (80,81). Dynamic methods have also been shown to reveal relationships with BMI and behavior where static methods were unable to (56). CAPs, in particular, identify critical co-activating patterns that recur across time by averaging time points with similar spatial distributions of brain activity at either the whole-brain or region-of-interest level (82). Further, CAPs require the specification of fewer assumptions than sliding window methods as they do not rely on arbitrary definitions of window size. CAPs have also been utilized to study neuropsychiatric disorders such as autism (64,83,84) and dynamic network changes across the lifespan (Kupis et al. 2021). Despite the advantages to using dynamic MRI methods over static MRI methods, no study to date has examined dynamic brain network alterations during rest across BMI or its association with EF. Further, exploring relationships among brain networks using brain dynamics has shown to be beneficial for the study of EF due to the various networks underlying EF (55).

This study aims to explore BMI as a moderator of the relationship between whole-brain CAP dynamics and EF, indexed by latent factors of shifting, fluency, and inhibition, using structural equation modeling (SEM). Examination of the dynamic interactions among the M-CIN, L-FPN, and M-FPN has provided important information about the network interactions subserving cognition; however, large-scale network interactions with other brain regions, such as the visual network, also lend insight into flexible cognition (85). Therefore, whole-brain network co-activations were assessed in this study. We hypothesized that a higher BMI would be associated with an altered relationship between brain network dynamics among the M-CIN, M-FPN, and L-FPN and shifting, an index of cognitive flexibility (34).

METHODS

Participants

This study included a sample of 253 adults (18–45 years) from the publicly available Nathan Kline Institute—Rockland Sample (http://fcon_1000.projects.nitrc.org/indi/enhanced/). Inclusionary criteria were as follows: (1) available neuroimaging and behavioral data, (2) no current Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnosis, and (3) mean framewise displacement (FD) < 0.5 mm (**Table 1**). Institutional Review Board approval was obtained for this project, and written informed consent was obtained for all study participants.

MEASURES

Body Mass Index

BMI was calculated from weight in kilograms divided by height in meters squared (kg/m^2) for all participants. Weight and height were measured during the study visit

Table 1. Participant Demographics

	N = 253 mean ± SD (minimum – maximum)
BMI (kg/m^2)	26.95 ± 5.90 (16.26 – 49.96)
Age (years)	28.44 ± 7.55 (18.15 – 44.82)
Mean FD (mm)	0.23 ± 0.09 (0.08 – 0.49)
Sex	105 M/ 148 F
DF Switching	8.59 ± 2.94 (1.00 – 16.00)
TMT	9.97 ± 2.83 (1.00 – 15.00)
VF Switching	10.47 ± 3.56 (1.00 – 19.00)
CWIT Inhibition	10.26 ± 2.89 (1.00 – 16.00)
CWIT Inhibition/Switching	9.89 ± 3.04 (1.00 – 14.00)
Tower Total Achievement	9.99 ± 2.36 (2.00 – 19.00)
VF Letter Fluency	10.61 ± 3.44 (1.00 – 19.00)
VF Category Fluency	11.28 ± 3.64 (2.00 – 19.00)
DF Composite Score	10.42 ± 2.69 (4.00 – 18.00)

Note: BMI, body mass index; FD, framewise displacement; DF, Design Fluency; TMT, Trail Making Test; VF, Verbal Fluency; CWIT, Color-Word Interference Test.

by study staff. Participants ranged in their BMI from underweight (<18.5 BMI), healthy weight (18.5 to <20 BMI), overweight (25 to <30 BMI), and obese (30 or higher BMI). For the purpose of this study, overweight/obesity are discussed interchangeably. See **Figure S1** for a graphical distribution of BMI in this sample.

Shifting

The D-KEFS was administered to all participants (1). The tasks with shifting (an index of cognitive flexibility) conditions within the D-KEFS include the Trail Making Test (TMT), the Design Fluency (DF) Test, and the Verbal Fluency (VF) Task. The TMT consists of five conditions, including the Number-Letter Switching condition (86). During the Number-Letter Switching condition, subjects switch back and forth between connecting numbers and letters (i.e., 1, A, 2, B, etc.) (87). The DF test consists of three conditions including a Switching condition. In the Switching condition, participants are asked to alternate between connecting empty and filled dots. Lastly, the VF test consists of three conditions, including the Category Switching condition. During the Category Switching condition, participants alternate between saying words from two different semantic categories.

Inhibition

The D-KEFS tasks with inhibition conditions included the Color-Word Interference Test (CWIT) and the Tower Test. The CWIT is a modified Stroop task and consists of four conditions including an inhibition and inhibition/switching condition. In the CWIT Inhibition condition, the participant is presented with color names that are written in incongruent ink color. The participant is required to name the ink color and ignore the written word. Therefore, participants have to inhibit saying the more automatic written word response. In the Inhibition/Switching condition, participants are presented with a page containing the words "red," "green," and "blue," written in red, green, or blue ink. Some of the words are contained in a box, and the subject must switch between saying the color of the ink (word is not inside a box) or the color of the word (word inside a box). The Tower Test examines the participant's ability to plan and carry out steps to attain the desired goal.

Fluency

The D-KEFS tasks with fluency conditions included the VF test and the DF test. The fluency measures in the VF test include the Letter Fluency and Category Fluency conditions. In both conditions, participants must generate as many words as possible within 60 seconds, beginning with either a specific letter or within a specific category. The DF test included trials where participants had to connect either empty or filled dots.

MRI Protocol

Three-dimensional magnetization-prepared rapid gradient-echo imaging (3D-MP-RAGE) structural scans and multiband (factor of 4) EPI-sequenced resting-state fMRI (rsfMRI) were acquired using a Siemens TrioTM 3.0 T MRI scanner. Scanning parameters were as follows: TR = 1400 ms, 2 × 2 × 2 mm, 64 interleaved slices, TE = 30 ms, flip angle = 65 degrees, field of view (FOV) = 224 mm, 404 volumes. Participants were instructed to keep their eyes open and fixate on a cross in the center of the screen during the 9.4-minute rsfMRI scan. For detailed MRI protocol information, see http://fcon_1000.projects.nitrc.org/indi/pro/nki.html.

Preprocessing and Postprocessing

Preprocessing steps were conducted using the Data Preprocessing Assistant for Resting-State fMRI Advanced edition (DPARSF-A; (88)), which uses FMRIB Software Library (FSL) and Statistical Parametric Mapping (SPM)-12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/), and were as follows: removal of the first five volumes to allow scanner signal to reach equilibrium, despiking, realignment, normalization directly to the 3 mm Montreal Neurological Institute (MNI) template, and smoothing (6 mm Full Width at Half Maximum (FWHM)).

Independent component analysis (ICA) was conducted using FSL's MELODIC by means of automatic dimensionality estimation. The ICA-FIX classification algorithm was applied to the data (FMIRB's ICA-FIX; (89)) using a subset of the participants to train FIX. ICA-FIX then classified ICA into noise and non-noise components for the rsfMRI data for individual subjects. The fMRI data also underwent nuisance covariance regression (linear detrend, Friston 24 motion parameters, global mean signal), despiking using AFNI's 3dDespike algorithm, and bandpass filtering (0.01–0.10 Hz). Information about the data processed without global mean signal regression is included in **Supplementary Materials**.

Parcellation

A 400 node parcellation was used containing nodes within 17 networks ((90); https://github.com/ThomasYeoLab/CBIG/tree/master/stable_projects/brain_parcellation/Schaefer2018_LocalGlobal). The parcellation incorporates local gradient and global similarity approaches from task-based and resting-state functional connectivity.

Co-activation Pattern Analysis

The time series were extracted from the 400 nodes for each subject and were converted to *z*-statistics and concatenated into one (nodes × timepoints) matrix (where the number of timepoints is 399 TR × 253 subjects).

The matrix was then subjected to *k*-means clustering to determine the optimal number of clusters. The elbow criterion was applied to the cluster validity index (the ratio between within-cluster to between-cluster distance) for values of k = 2–20, and an optimal value of k = 5 was determined (**Figure S2**).

K-means clustering (squared Euclidean distance) was then applied to the matrix using the optimal k = 5 to produce five CAPs ("brain states"). CAP metrics were calculated and included: (a) dwell time (DT), calculated as the average number of continuous TRs that a participant stayed in a given brain state, (b) frequency of occurrence of brain states, calculated as an overall percentage that the brain state occurred throughout the duration of rsfMRI scan compared to other brain states, and (c) the number of transitions, calculated as the number of switches between brain states.

Statistical Analysis

The normative data were age-corrected for all D-KEFS variables. All data were screened for outliers, missingness in data, and tests of assumptions (see **Supplementary Materials** for more information about the assumptions). Additionally, each CAP was assessed prior to statistical modeling to determine if the brain regions co-activated in each CAP had theoretical support behind including the CAP in the models. Using a two-step procedure, a measurement model was evaluated first to ensure an acceptable fit for the data, and then a structural moderated model was examined. Confirmatory factor analysis (measurement model) and SEM were conducted in MPlus (91,92) using maximum likelihood to estimate model parameters and full information maximum likelihood approach to allow data to be included regardless of the pattern of missingness in the data. Code for all MPlus analyses is publicly available (https://github.com/lkupis/NKI_BMI). Covariates included mean FD, age, and sex. All models were assessed for the goodness of fit by examining the following: χ^2, comparative fit index (CFI), standardized root-mean-square residual (SRMR), and root-mean-square error of approximation (RMSEA). $\chi^2 > .05$, CFI $\geq .95$, SRMR values $\leq .08$, and RMSEA values $\leq .06$ indicated good model fit.

Confirmatory Factor Analysis

A three-factor model was tested based on prior findings of a three-factor model using the D-KEFS (33). The three factors were shifting, inhibition, and fluency. Additionally, all indicators used were scaled or age-adjusted scores (M = 10, SD = 3).

The indicators for shifting included the TMT Number-Letter Switching condition, the DF Switching condition, and the VF Switching condition scores. The shifting indicator in the TMT condition was the Number-Letter Switching-total score or time to completion. The shifting indicator in the DF Switching condition was the Switching Total Correct score or the number of unique designs drawn. The shifting indicator in the VF test was the total correct number of category switches made.

The indicators for inhibition included the CWIT Inhibition and Inhibition/Switching conditions and Tower total achievement score. The inhibition indicator for the CWIT Inhibition condition was the total number of correct responses. The inhibition indicator in the Tower Test was the Total Achievement score or the sum of points given in each trial. The CWIT shifting indicator included the total score for the number of correct switches made. Although the Inhibition/Switching condition could also potentially be used as an indicator for the shifting factor, previous work has found it to be involved in inhibition using the SEM framework (33).

The fluency indicators included the VF letter and category fluency scores, and the DF total composite score. The fluency indicators in the VF test included the Letter Fluency Total Correct score and the Category Fluency Total correct scores. The fluency indicator from the DF test was the total unique designs drawn across the two DF trials.

The three-factor model including shifting, inhibition, and fluency was evaluated first for statistical fit, and one- and two-factor models were evaluated thereafter because of previous theoretical evidence supporting both the unity and diversity of EFs (23). The one-factor model included all indicators under one factor or a "common EF." Three two-factor models were tested with three combinations of the latent factors (i.e., shifting with inhibition; shifting with fluency; inhibition with fluency). The proposed model is presented in **Figure 1**.

Structural Model

The best-fitting model from the confirmatory factor analysis was tested within the framework of SEM. The latent variable(s) in the model were the dependent variables in the SEMs. The use of SEMs has been growing within the field of cognitive neuroscience (93) and brain dynamic analyses (94). First, BMI was tested as a moderator between each brain dynamic metric (DT, frequency of occurrence, and transitions) for each of the five CAPs and the latent variable (shifting, inhibition, or fluency) in an exploratory analysis. A moderator is a variable thought to affect the relationship between two other variables (68). A moderator was tested because there is previous evidence that brain dynamics support EF (55,64); however, the results were not consistent across all EFs suggesting the relationship between brain dynamics and EF may be dependent on a third variable for specific EFs. BMI was tested as the moderator due to previous work suggesting a link between brain dynamics and EF, and previous evidence that functional

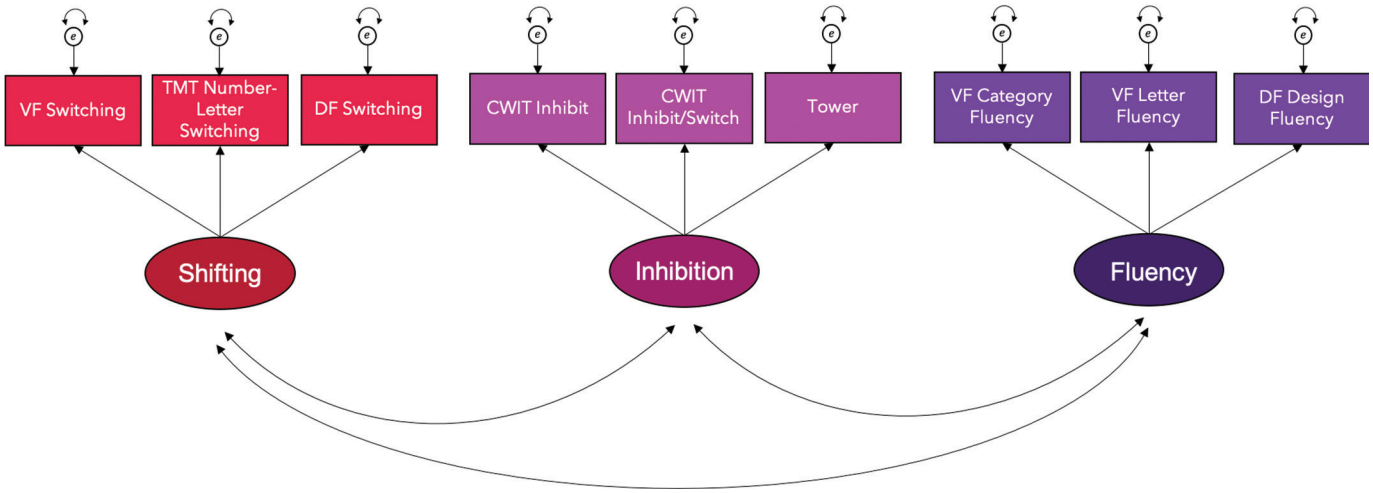


Fig. 1. Confirmatory factor analysis. The proposed three-factor measurement model. VF, Verbal Fluency; TMT; Trail Making Test; DF, Design Fluency; CWIT, Color-Word Interference Test.

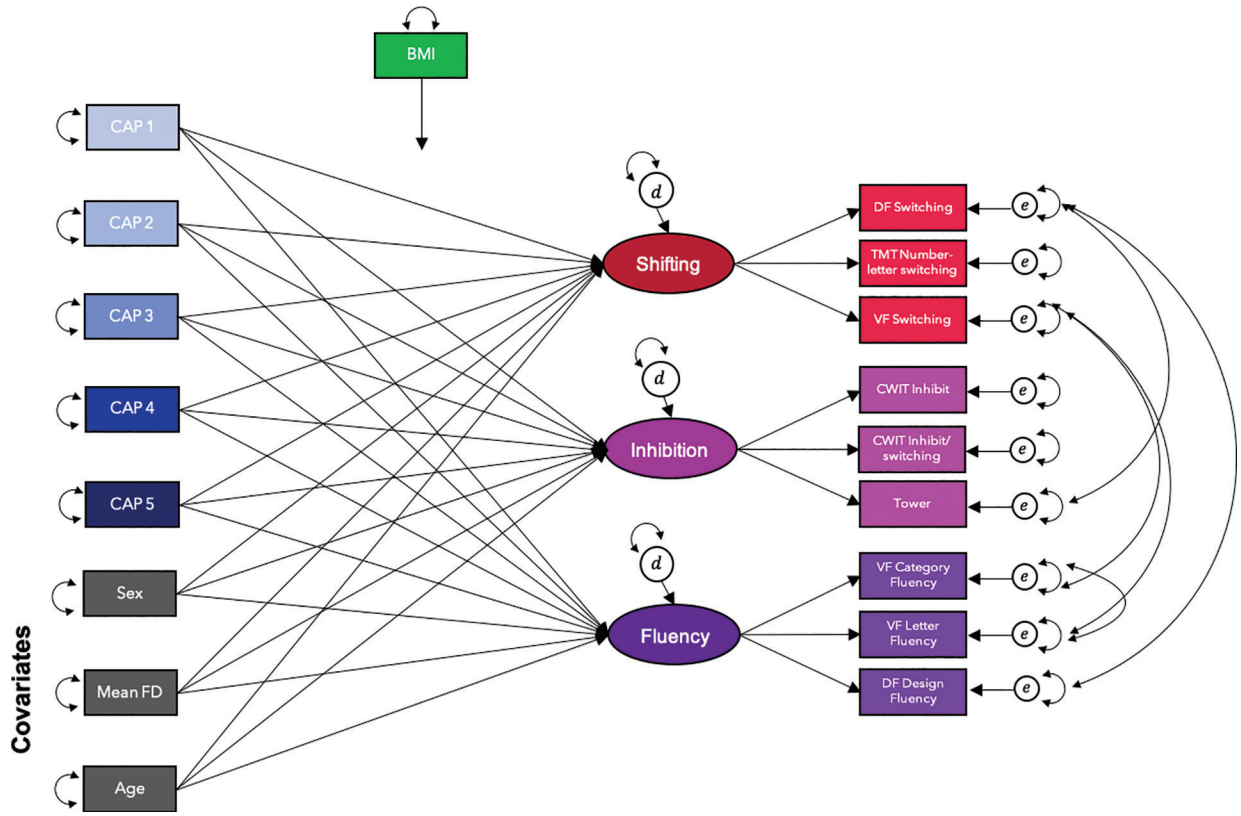


Fig. 2. Structural equation model. Structural equation model linking co-activation patterns (CAPs) with executive function (shifting, inhibition, and fluency) moderated by body mass index (BMI).

connectivity may give rise to poorer EF at certain levels of BMI, primarily in overweight/obese individuals (37,95). Additionally, the use of a moderator is beneficial when the relationships among variables are equivocal (70), as in BMI, brain dynamics, and EF (11,37). BMI and the brain dynamic metrics were mean centered to reduce multicollinearity (96).

The interactions were tested separately to reduce the effects of multicollinearity and negative impacts on parameter estimations (97). Accordingly, each latent factor outcome was tested while retaining all latent factors in the model due to best model fit; however, they were predicted one at a time with the main effects and covariates as depicted in **Figure 2**. Variables without a significant interaction were tested for main effects using the SEM framework. Significant interactions indicate that the effect observed between the independent variable and dependent variable is dependent on a moderating variable (98,99). As in previous work (64,100,101), only variables within nonsignificant

interactions were tested for main effects as these variables were not dependent on BMI. Covariates included mean FD, age, and sex following prior work (102–104). For significant interactions, simple slope analyses were conducted using the Johnson-Neyman technique (105) at various standard deviations (i.e., +1/−1 SD from the mean) for BMI to provide regions of significance.

Further, significant results for the moderation analyses were recomputed without BMI outliers and with bootstrapping. The outlier and bootstrapping analyses can be found in **Supplementary Materials**. To minimize type II error when performing a moderation in SEM, an α-value of $p < .05$ was selected. All code for the fMRI and statistical analytic steps can be viewed on GitHub (https://github.com/lkupis/NKI_BMI).

RESULTS

Co-activation Patterns

Five dynamically recurrent brain states were observed across the participants (**Figure 3**). CAP 1 was characterized by co-activation among the visual network. CAP 2 was characterized by co-activation among the L-FPN, M-FPN, and limbic nodes. CAP 3 was characterized by co-activation among the M-FPN. CAP 4 was characterized by co-activation among the L-FPN, DAN, limbic, and M-CIN nodes. Lastly, CAP 5 was characterized by co-activation among the D-FPN, M-CIN, somatosensory motor, and visual network nodes. See a graphical presentation of the CAPs in **Figure 3**; frequency of occurrence of each CAP can be seen in **Table S3**; and maps of each CAP can be downloaded from Neurovault (https://www.neurovault.org/collections/10019/).

The co-activation patterns (CAPs) show brain regions that are activated or de-activated together. The graphical depiction of each CAP is shown in the brain images on the left. L-FPN, lateral frontoparietal; M-FPN, medial frontoparietal; D-FPN, dorsal frontoparietal; M-CIN, mid cinguloinsular; SomMot, somatosensory motor.

Statistical Analyses

Outliers were identified in BMI; however, the values represented physiologically obtainable values so they were retained. The average percentage of missing data was .1% and tests for normality indicated all variables approximated a normal distribution.

Confirmatory Factor Analysis

Several models were tested including a three-factor model with shifting, inhibition, and fluency latent factors, a one-factor model including all indicators as one EF factor and three two-factor models (shifting and inhibition, shifting and fluency, and inhibition and fluency). Examination of the three-factor model after the inclusion of residual covariances between indicators indicated good model fit, $\chi^2 = 19.52$ (df = 19, $p = .424$), CFI = 1.00, SRMR = .03, and RMSEA = .01. The one-factor model indicated poor model fit, $\chi^2 = 45.09$ ($df = 22$, $p = .003$), CFI = .96, SRMR = .05, and RMSEA = .07. Results of the two-factor models are in **Table S1**. All two-factor models indicated poorer model fit compared with the three-factor model, thus confirming the *a priori* three-factor model (33).

The three-factor model included three latent factors of shift, inhibition, and fluency, and each factor

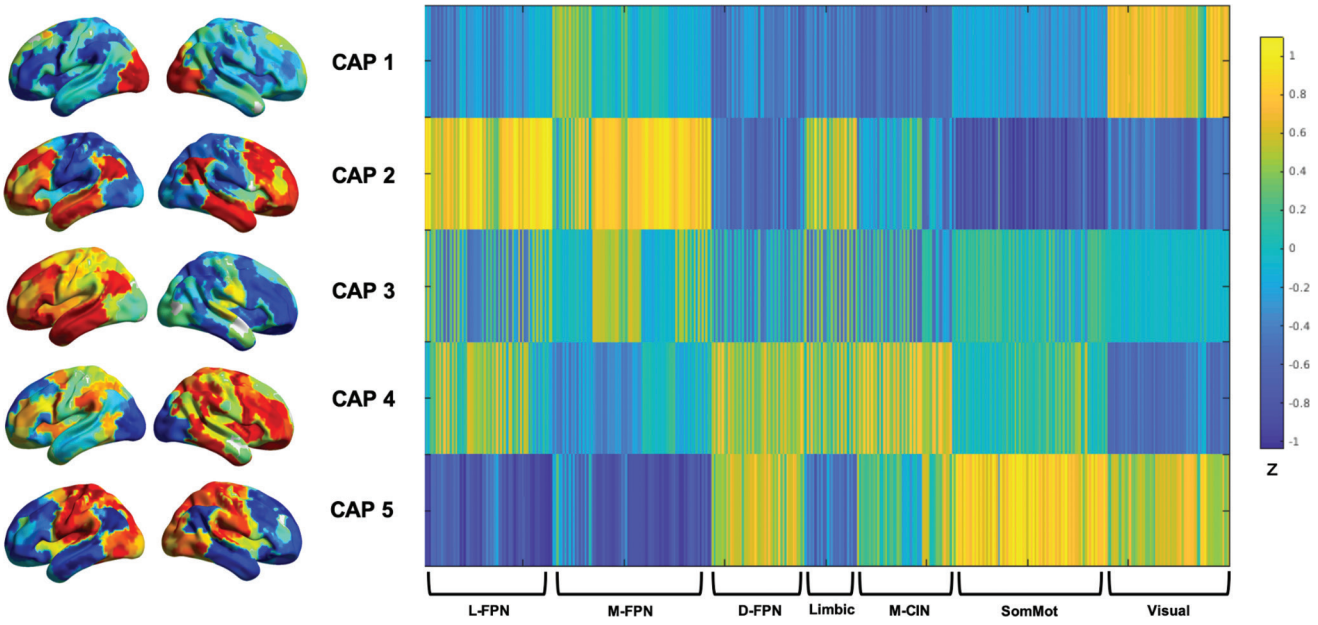


Fig. 3. Recurring co-activation patterns.

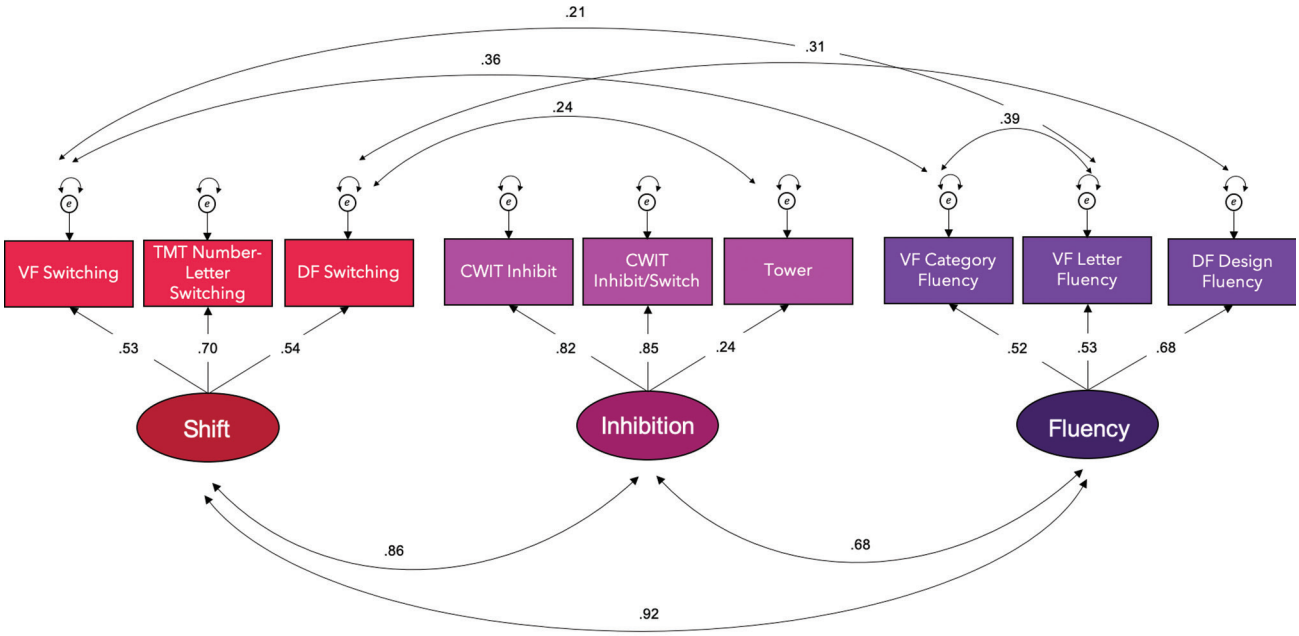


Fig. 4. **Final three-factor measurement model.** VF, Verbal Fluency; TMT; Trail Making Test; DF, Design Fluency; CWIT, Color-Word Interference Test.

Table 2. Summary of Three-Factor Measurement Model Pathways

	β	b	SE	p	95% CI [lower 2.5%, upper 2.5%]
Shifting					
1. TMT	.70	1.00	.00		[1.00, 1.00]
2. DF Switch	.54	.80	.12	<.001***	[.57, 1.02]
3. VF Switch	.53	.95	.14	<.001***	[.68, 1.22]
Inhibition					
1. CWIT Inhibition	.85	1.00	.00		[1.00, 1.00]
2. CWIT Inhibition/Switch	.82	1.01	.09	<.001***	[.84, 1.18]
3. Tower	.24	0.23	.07	<.001***	[.09, .36]
Fluency					
1. VF Letter	.53	1.00	.00		[1.00, 1.00]
2. VF Category	.52	1.02	.16	<.001***	[.71, 1.33]
3. DF Fluency	.68	1.00	.18	<.001***	[.65, 1.35]

***p < .001.

had three indicators. The three-factor model was first tested without residual covariances. However, upon examination of the residual and modification indices, five residual covariances were identified (**Figure 4**). All the factor loadings were significant (p's < .001; see **Figure 4**). Additionally, all standardized factor loadings were >.5, except for the Tower indicator for Inhibition (.24). However, the Tower indicator was retained due to theoretical evidence supporting it as an indicator for inhibition (106). See **Table 2** for the results of the three-factor measurement model.

The three-factor variables were significantly correlated with each other (p's < .001; see **Figure 4**). Examination of the estimates of the correlations between pairs of residuals revealed various significant correlations (p's < .01; **Figure 4**). Previous work suggests that different EFs are correlated yet separable (22,33).

Structural Models

Several structural models were conducted involving the interactions between BMI and the brain dynamic metrics for each CAP predicting shifting, inhibition, and fluency. The interactions were tested one at a time while predicting one latent factor at a time.

Table 3. Summary of Interactions

	β	*B*	*SE*	95% CI [lower 2.5%, upper 2.5%]	R^2
Shifting					
BMI × DT CAP 1	−.05	−.03	.03	[−.09, .03]	.05
BMI × DT CAP 2	.12	.05	.03	[.01, .23]	.06
BMI × DT CAP 3	−.05	−.03	.03	[−.08, .03]	.05
BMI × DT CAP 4	.05	.02	.02	[−.03, .07]	.05
BMI × DT CAP 5	.14	.06	.02	[.01, .11]	.06
BMI × F CAP 1	−.04	−.35	.50	[−1.34, .63]	.05
BMI × F CAP 2	.08	.67	.47	[−.24, 1.59]	.05
BMI × F CAP 3	−.09	−.74	.45	[−1.62, .14]	.04
BMI × F CAP 4	.01	.11	.50	[−.88, 1.09]	.04
BMI × F CAP 5	.05	.43	.48	[−.52, 1.37]	.05
BMI × Transitions	−.09	−.003	.002	[−.01, .001]	.05
Inhibition					
BMI × DT CAP 1	−.001	−.001	.04	[−.08, .07]	.04
BMI × DT CAP 2	−.12	−.07	.03	[−.13, −.003]	.05
BMI × DT CAP 3	.08	.05	.03	[−.02, .12]	.04
BMI × DT CAP 4	−.03	−.02	.03	[−.08, .04]	.04
BMI × DT CAP 5	−.11	−.06	.03	[−.11, .003]	.05
BMI × F CAP 1	.06	.72	.64	[−.53, 1.97]	.04
BMI × F CAP 2	−.09	−.89	.59	[−.19, .25]	.04
BMI × F CAP 3	.09	.89	.57	[−.22, 2.01]	.05
BMI × F CAP 4	−.04	−.46	.65	[−.15, .07]	.04
BMI × F CAP 5	−.03	−.36	.62	[−.14, .08]	.04
BMI × Transitions	.07	.003	.002	[−0.002, 0.01]	.04
Fluency					
BMI × DT CAP 1	.08	.04	.04	[−.03, .11]	.01
BMI × DT CAP 2	−.04	−.02	.03	[−.07, .04]	.01
BMI × DT CAP 3	−.01	−.004	.03	[−.06, .06]	.01
BMI × DT CAP 4	.12	.05	.03	[−.01, .25]	.02
BMI × DT CAP 5	−.07	−.03	.03	[−.07, .02]	.01
BMI × F CAP 1	−.02	−.21	.58	[−1.35, .92]	.01
BMI × F CAP 2	−.06	−.48	.53	[−1.51, .56]	.02
BMI × F CAP 3	.40	.40	.51	[−.60, 1.40]	.02
BMI × F CAP 4	.11	.96	.60	[−.22, 2.13]	.02
BMI × F CAP 5	−.08	−.65	.56	[−1.75, .44]	.01
BMI × Transitions	−.02	−.001	.002	[−.01, .003]	.01

CI, confidence interval; DT, dwell time; F, frequency; BMI, body mass index.

Interactions

Results from the moderation SEM models can be seen in Table 3. When the individual interactions predicted each latent factor, three significant interactions were present. First, there were significant interactions between BMI and CAP 2 (characterized by co-activation among the L-FPN, M-FPN, and limbic nodes) DT predicting shifting, $\beta = .12$, $b = 0.05$, $SE = 0.03$, 95% CI [0.01, 0.23], and inhibition, $\beta = -.12$, $b = -0.07$, $SE = 0.03$, 95% CI [−0.13, −0.003].

There was also an interaction between BMI and CAP 5 (characterized by co-activation among the DAN, M-CIN, somatosensory motor, and visual network nodes) DT predicting shifting, $\beta = .14$, $b = 0.06$, $SE = 0.02$, 95% CI [0.01, 0.11].

All interactions accounted for statistically significant proportions of variance in each latent factor (**Table 3**), respectively, 6%, 5%, and 5%. Additionally, all reported interactions were reanalyzed without BMI outliers and with bootstrapping and only significant interactions with shifting remained (see **Supplementary Materials**).

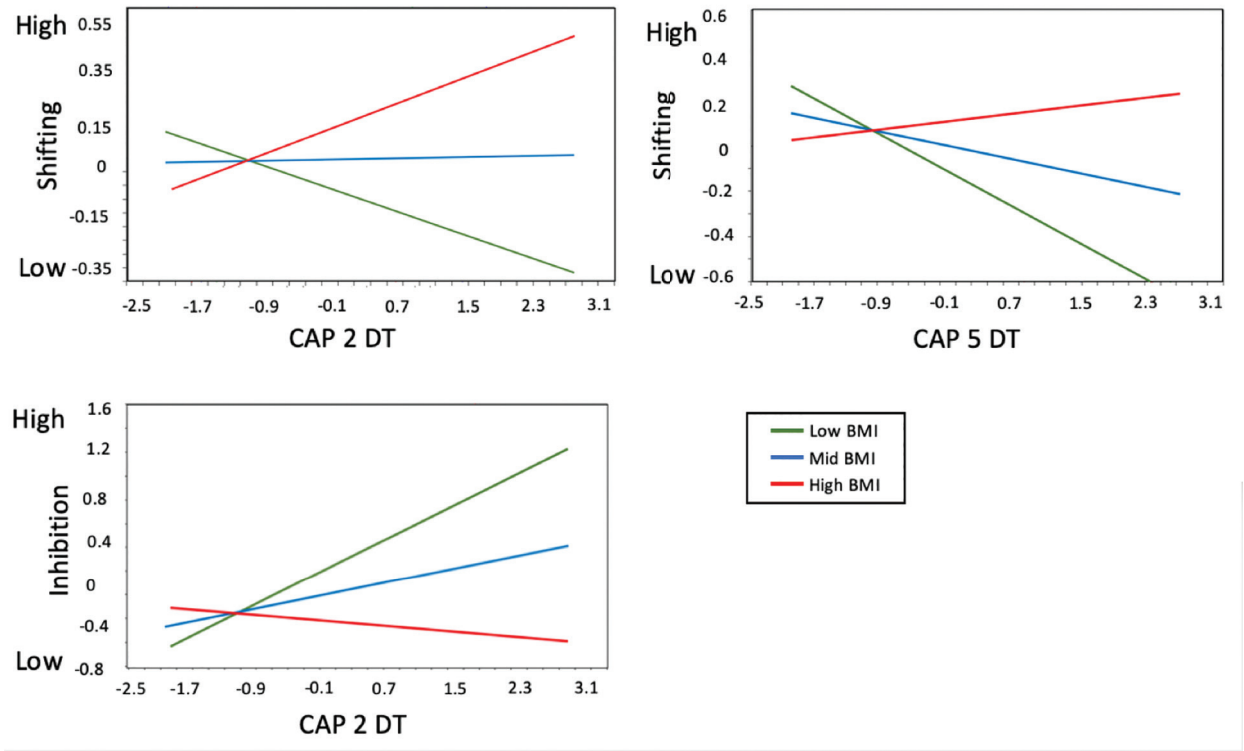


Fig. 5. Simple slopes.

The reported interactions were further probed using the Johnson-Neyman technique to generate regions of significance plots in Mplus (**Figure S4**). The results showed that for all reported BMI × CAP DT interactions predicting shifting and inhibition, significance was reached at average and high levels of BMI (0–5 *z*-scores). Further, at higher levels of BMI, an increase in CAP DTs was associated with an increase in shifting. The opposite relationship was shown in average and low BMI. However, for inhibition, at higher levels of BMI, an increase in CAP DTs was associated with a decrease in inhibition (**Table S2; Figure 5**). Overall, a high BMI was associated with an altered pattern between brain network dynamics and executive functioning.

The moderating effect of body mass index (BMI) on the relationship between co-activation pattern dynamics (DT and transitions) and executive functions. All variables were standardized, so a score of 0 represents the average.

Main Effects

Nonsignificant interactions were followed up by testing for main effects. There was a main effect for DT of CAP 1 (characterized by co-activation among the visual network) predicting inhibition, $b = -0.83$, $SE = 0.41$, 95% CI [−1.64, −0.02]. There were no other significant main effects as depicted in **Table S4**.

DISCUSSION

Overweight/obesity is associated with far-reaching negative impacts including health comorbidities (6), executive dysfunction (15), brain structural and functional alterations (107), and poor mental health (28). However, it is unknown whether or not BMI moderates the relationship between brain network dynamics and EF.

This study explored BMI as a moderator of whole-brain network dynamics and EF using a dynamic CAP analysis. We first assessed a measurement model consisting of shifting, inhibition, and fluency latent factors and found a three-factor model best fit the data. Next, latent factors of EF were used as dependent measures within a moderation SEM. Latent factors as dependent variables reduce the task impurity problem, and a latent variable is thought to be a purer measure of the target ability with reduced measurement error (31). We found BMI moderated the relationship between (1) DT of CAP 2 (L-FPN, M-FPN, and limbic) predicting shifting and (2) DT of CAP 5 (D-FPN, M-CIN, somatosensory motor, and visual) predicting shifting. In significant interactions predicting shifting, at higher levels of BMI, an increase in CAP DTs was associated with an increase (higher score) in shifting. The opposite, and expected relationship, was shown in average and low BMI. Together, these findings suggest that there is an altered relationship between brain network dynamics and EF in overweight/obesity.

Currently, there is one study to our knowledge that has examined brain network dynamics across BMI (56). Few studies have assessed task fMRI brain activation and rsfMRI functional connectivity in overweight/obese individuals (37). The limited literature supports weight-related alterations in the M-CIN, M-FPN, and L-FPN (37). Overweight/obese individuals have been most commonly reported to have weakened connectivity among nodes within the L-FPN (39) and enhanced connectivity among nodes within the M-CIN (108) and M-FPN (44,109). Consistent with this work, in all significant interactions between BMI and brain network dynamics, we found CAPs consisting of the L-FPN, M-FPN, and M-CIN. This suggests that there are alterations among brain regions involved in executive functioning, internal thoughts, and salience processing (46) in individuals with a higher BMI.

Although there is limited information regarding the mechanisms surrounding executive dysfunction and brain dynamic alterations associated with an increased BMI (11), prior work suggests bidirectional relationships among BMI, cognition, and brain structure and function (11,37). For example, weight loss has been shown to have positive impacts on cognition (110) and is associated with brain structural and functional changes (111,112). Additionally, there is evidence that functional differences associated with overweight/obesity among brain regions that support EF, notably among and within the L-FPN, M-FPN, and M-CIN, may contribute to executive dysfunctioning and potentially contribute to a higher BMI (37). Our results additionally suggest that alterations among the L-FPN, M-FPN, and M-CIN may contribute to differences seen in EF in overweight/obesity and extends prior work by revealing that the relationship between brain dynamics and EF is moderated by BMI during young- to middle-aged adulthood.

The literature also suggests that brain alterations associated with a higher BMI are not only seen among the three large-scale brain networks but also with other regions important for sensory, emotional, and reward processing (44,50,113–116). Increased functional connectivity has also been shown in regions of the D-FPN in obese individuals (39), suggesting alterations are in top-down control of attention (117). Similarly, in this study and in the instances where CAP relationships with EF depended on BMI, the co-activations also consisted of the limbic, D-FPN, somatomotor, and visual networks. Since the CAP relationships predicting EF were altered in a higher BMI, this suggests that top-down and bottom-up processes are also altered, consistent with previous findings. However, this study extends prior research by assessing CAPs associated with EF and the moderating effect of BMI on those pathways. Together, alterations among the large-scale networks and visual, sensorimotor, D-FPN, and limbic networks associated with EF may further perpetuate a higher weight in individuals with a higher BMI.

Previous work suggests that greater neural flexibility is associated with greater cognitive performance (71,118–120). In a study that examined brain dynamics in 19- to 80-year olds, DT increased with age and age was negatively correlated with total scores on the Wechsler Adult Intelligence Scale (WAIS) (120). This suggests that a longer time spent in certain states may be associated with poorer cognition. Consistent with this notion, in most of the significant interactions between BMI and DT, we found at average and lower BMIs, there was a negative relationship between the CAP DTs and shifting, suggesting as DT increases, shifting abilities worsen. However, opposite patterns among DT and shifting were observed in individuals with a higher BMI compared to individuals with average and lower BMIs, indicating in overweight/obese individuals, a shorter DT is associated with poorer shifting abilities. Prior evidence supports that global brain network integration is needed for effective cognitive performance (121). A potential reason underlying the differences in individuals with a high BMI may be that brain networks may not be well integrated, as supported by altered functional connectivity (37–39,45,50) and, therefore, associated with poorer EF. Additionally, prior work has shown that obese individuals exhibit reduced global and local network efficiency compared with healthy-weight individuals (122) potentially underlying the differences observed in brain dynamics. Global and local network efficiency has also been previously linked with cognitive performance (123,124); however, this needs to be further explored in overweight and obese individuals. Overall, our findings support altered brain dynamic relationships with shifting and inhibition in individuals with a high BMI.

Lastly, it is important to note that we obtained primarily significant interactions between BMI and CAP dynamic metrics associated with shifting in this study and one main effect result. Significant interactions indicate that the effect observed between the independent variable and dependent variable is dependent on a moderating variable (98,99). In this study, the relationship between brain dynamics and shifting depends on the BMI of the individual. For example, when we examined the effect of shifting on brain dynamics, the effect was significant only at average to high BMI values but not for low BMI values (**Figure S4**). Therefore, the main effects for those specific variables become unimportant since the relationship is dependent on BMI. For nonsignificant interactions, the main effects were tested since there was evidence that the relationship between brain dynamics and EF was not dependent on BMI as done in previous studies (64,100,101).

We also found one main effect such that the brain dynamics of the visual network was associated with inhibition. Previous work has revealed associations between the visual network and cognition (125,126), suggesting information flow from sensory regions may influence higher-order processes. Interestingly, the relationship between visual network dynamics and inhibition was not dependent on BMI in this study. The visual network

and sensorimotor areas develop earlier, and regions important for higher-order cognitive functions undergo fine-tuning across development (127). Additionally, interactions between sensory areas and cognition are shaped across development, creating more efficient task responses to stimuli (128,129). Since this study only included young- to middle-aged adults, it is difficult to establish whether processes underlying sensory–cognitive interactions may be impacted by BMI differently across the lifespan. Therefore, longitudinal studies across the lifespan are needed to uncover the relationships among sensory regions, cognition, and BMI.

The mechanisms supporting brain-related changes in overweight/obese individuals and the associated executive dysfunction remain elusive (11,37). There are various hypotheses that may contribute to our findings of altered brain dynamic relationships with EF in individuals with a high BMI. As previously mentioned, weight loss has been shown to be associated with changes in cognition and functional connectivity (37), suggesting weight is mechanistically linked with cognition and brain function. Potential hypotheses accounting for this mechanism have been suggested and include greater leptin levels (130) and resistance (131), higher levels of inflammatory markers (132,133), impaired insulin regulation (134), impaired blood–brain barrier dysfunction (133), and elevated triglycerides in overweight/obese individuals (11). For example, individuals with obesity have been found to be in a low-grade proinflammatory state (11). Certain inflammatory markers have been linked with cognitive decline (11,133,135,136), and sustained inflammation has been linked with neurodegeneration (137). Although these hypotheses reveal potential mechanisms to explain the relationships among BMI, brain dynamics, and EF, future work is needed to further explore these relationships in humans and longitudinally using mediation models.

As previously noted (39), many neuropsychiatric disorders are characterized by alterations among the same networks as overweight/obese individuals, markedly the M-CIN, M-FPN, and L-FPN. For example, in autism spectrum disorder (ASD), there are mixed findings using functional connectivity that are often attributed to the heterogeneous nature of the disorder (138). Although that is an attributing factor, many studies have not controlled for BMI (83,84,139–142). Further, recent work suggests that ASD should be studied in the context of heterogeneity but does not attribute BMI as a potential contributor (143), despite greater rates of overweight/obesity in ASD (144,145). In one study where BMI was accounted for a while examining brain dynamic differences in ASD and neurotypical individuals, brain differences were seen in ASD individuals based on their BMI (64). Our findings further support the notion that BMI may in part contribute to the differences seen between neurotypical populations and individuals with ASD. Therefore, BMI should be accounted for when exploring brain dynamic differences in heterogeneous, neuropsychiatric conditions.

Some limitations are important to note in this study. First, BMI is considered an acceptable measure to study weight-related differences; however, it does not take into account adiposity or muscle leanness. Additionally, although the sample size included is one of the largest to assess brain relationships with BMI, future studies should continue to utilize larger samples to increase the generalizability of the results. Our sample also included fewer underweight individuals than healthy weight and overweight/obese individuals (**Figure S1**) and may account for the lack of significant results found in underweight individuals. Future studies should include a larger sample of underweight individuals. Additionally, as it is more difficult to observe an effect with interactions (95,146), our results were not Bonferroni or FDR corrected. Further, by not adjusting for multiple comparisons, the results in this study may include increased false positives. Therefore, future work is needed to replicate the findings. Further, not all tests were available as part of the D-KEFS for this particular sample. For example, a common shifting task is the Wisconsin Card Sorting Test (147); however, very few participants were given this test, and therefore, it was not included. Similarly, the CWIT Inhibition/Switching condition was used as an inhibition indicator in this study; however, this indicator may additionally recruit shifting abilities. Therefore, the psychometric properties of the D-KEFS should be further explored. Lastly, the latent factors assessed were highly correlated. Although the measurement models tested indicated separable factors, there may still be overlap within the factors tested as previous work suggests EFs are correlated yet separable (22). Further, in previous studies (55,64), shifting abilities but not other EFs have been associated with brain dynamic patterns. Similarly, our main findings were associated with shifting. When outliers were removed and bootstrapping was implemented, the results for inhibition were no longer significant. Further work is needed to investigate this phenomenon. Additionally, future work should consider how different dynamic methods (e.g., sliding window; (148)) may uncover different aspects of brain function related to EF and BMI.

Future directions should be considered as a result of the findings from this study. In older age, having a higher BMI has been described as a "neuroprotective" factor and the "obesity paradox," where cognition is generally preserved (149), and life expectancy is increased (150). Moreover, there is evidence that being overweight in older adulthood (75–90 years) provides an advantage in episodic memory compared with normal-weight older adults (149), and this effect is potentially mediated by functional connectivity within the M-FPN. Future work is needed to explore the neuroprotective effect of a higher BMI in older adults and its relationship among brain dynamics and EF (i.e., cognitive flexibility, fluency/updating, and inhibition). To this end, future work is

additionally needed to explore BMI longitudinally and across the lifespan to gather further evidence of the mechanisms underlying cognitive and neural changes associated with overweight/obesity. Additionally, due to the cross-sectional nature of this study's sample, a mediation analysis was not tested (151–155). Growing evidence in children and older adult populations suggests that overweight/obesity may affect cognition through changes in brain structure (156,157). One suggested pathway underlying this mediation is through a low-grade inflammatory response characterized in obesity, shown to alter brain structure and cause EF impairments (15,158). Future work is needed to longitudinally disentangle the relationships among BMI, EF, and brain dynamics using mediation models. Lastly, in this study, CAP 3 exhibited laterality, and CAP 4 exhibited stronger co-activation on the left compared with the right hemisphere similar to findings in previous work (65,159–162). Future work is needed to better understand the relationship between CAP lateralization and EF.

In conclusion, we find evidence that BMI moderates the relationship between brain network dynamics among the M-CIN, M-FPN, and L-FPN as well as regions of the visual, D-FPN, sensorimotor and limbic regions, and shifting. Specifically, a higher BMI was associated with an altered mechanism of brain network dynamics associated with shifting. Our findings suggest that brain network dynamics underlying EF depend on BMI and that, in future studies, BMI should be considered when studying relationships between brain network dynamics and individual differences in cognition.

REFERENCES

1. Delis DC, Kaplan E, Kramer JH (2001): *Delis-Kaplan Executive Function System: D-KEFS*. APA PsycTests. https://doi.org/10.1037/t15082-000
2. 2015 GB of DS (2017): *Global Burden of Disease Study 2015 (GBD 2015) Obesity and Overweight Prevalence 1980–2015*. Seattle, WA: Institute for Health Metrics and Evaluation (IHME).
3. Hales CM, Carroll MD, Fryar CD, Ogden CL (2020): Prevalence of obesity and severe obesity among adults: United States, 2017–2018. Retrieved from https://stacks.cdc.gov/view/cdc/85451
4. World Health Organization and Others (2017): *Obesity and Overweight*. Geneva: World Health Organization.
5. Huang Y, Lu Y, Huang Y-M, Wang M, Ling W, Sui Y, Zhao H-L (2020): Obesity in patients with COVID-19: a systematic review and meta-analysis. *Metabolism* 113: 154378.
6. Singh GM, Danaei G, Farzadfar F, Stevens GA, Woodward M, Wormser D, *et al.* (2013): The age-specific quantitative effects of metabolic risk factors on cardiovascular diseases and diabetes: a pooled analysis. *PLoS One* 8: e65174.
7. Miller AA, Spencer SJ (2014): Obesity and neuroinflammation: a pathway to cognitive impairment. *Brain Behav Immun* 42: 10–21.
8. Rochette AD, Spitznagel MB, Strain G, Devlin M, Crosby RD, Mitchell JE, *et al.* (2016): Mild cognitive impairment is prevalent in persons with severe obesity. *Obesity* 24: 1427–1429.
9. Fitzpatrick AL, Kuller LH, Lopez OL, Diehr P, O'Meara ES, Longstreth WT Jr, Luchsinger JA (2009): Midlife and late-life obesity and the risk of dementia: cardiovascular health study. *Arch Neurol* 66: 336–342.
10. Bocarsly ME, Fasolino M, Kane GA, LaMarca EA, Kirschen GW, Karatsoreos IN, *et al.* (2015): Obesity diminishes synaptic markers, alters microglial morphology, and impairs cognitive function. *Proc Natl Acad Sci U S A* 112: 15731–15736.
11. Smith E, Hay P, Campbell L, Trollor JN (2011): A review of the association between obesity and cognitive function across the lifespan: implications for novel approaches to prevention and treatment. *Obes Rev* 12: 740–755.
12. Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry CP Jr, Yaffe K (2005): Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. *BMJ* 330: 1360.
13. Gunstad J, Paul RH, Cohen RA, Tate DF, Spitznagel MB, Grieve S, Gordon E (2008): Relationship between body mass index and brain volume in healthy adults. *Int J Neurosci* 118: 1582–1593.
14. Fitzpatrick S, Gilbert S, Serpell L (2013): Systematic review: are overweight and obese individuals impaired on behavioural tasks of executive functioning? *Neuropsychol Rev* 23: 138–156.
15. Yang Y, Shields GS, Guo C, Liu Y (2018): Executive function performance in obesity and overweight individuals: a meta-analysis and review. *Neurosci Biobehav Rev* 84: 225–244.
16. Diamond A (2013): Executive functions. *Annu Rev Psychol* 64: 135–168.
17. Doebel S (2020): Rethinking executive function and its development. *Perspect Psychol Sci* 15: 942–956.
18. Bailey CE (2007): Cognitive accuracy and intelligent executive function in the brain and in business. *Ann N Y Acad Sci* 1118: 122–141.
19. Madjar N, Chubarov E, Zalsman G, Weiser M, Shoval G (2019): Social skills, executive functioning and social engagement. *Schizophr Res Cogn* 17: 100137.
20. Leung RC, Vogan VM, Powell TL, Anagnostou E, Taylor MJ (2016): The role of executive functions in social impairment in Autism Spectrum Disorder. *Child Neuropsychol* 22: 336–344.
21. Brown TE, Landgraf JM (2010): Improvements in executive function correlate with enhanced performance and functioning and health-related quality of life: evidence from 2 large, double-blind, randomized, placebo-controlled trials in ADHD. *Postgrad Med* 122: 42–51.
22. Miyake A, Friedman NP (2012): The nature and organization of individual differences in executive functions: four general conclusions. *Curr Dir Psychol Sci* 21: 8–14.
23. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD (2000): The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: a latent variable analysis. *Cogn Psychol* 41: 49–100.
24. Testa R, Bennett P, Ponsford J (2012): Factor analysis of nineteen executive function tests in a healthy adult population. *Arch Clin Neuropsychol* 27: 213–224.
25. Morris L, Mansell W (2018): A systematic review of the relationship between rigidity/flexibility and transdiagnostic cognitive and behavioral processes that maintain psychopathology. *J Exp Psychopathol* 9: 2043808718779431.
26. Tavares JVT, Taylor Tavares JV, Clark L, Cannon DM, Erickson K, Drevets WC, Sahakian BJ (2007): Distinct profiles of neurocognitive function in unmedicated unipolar depression and bipolar II depression. *Biol Psychiatry* 62: 917–924.
27. van Vuuren CL, Wachter GG, Veenstra R, Rijnhart JJM, van der Wal MF, Chinapaw MJM, Busch V (2019): Associations between overweight and mental health problems among adolescents, and the mediating role of victimization. *BMC Public Health* 19: 612.
28. Simon GE, Von Korff M, Saunders K, Miglioretti DL, Crane PK, van Belle G, Kessler RC (2006): Association between obesity and psychiatric disorders in the US adult population. *Arch Gen Psychiatry* 63: 824–830.
29. Floyd RG, Bergeron R, Hamilton G, Parra GR (2010): How do executive functions fit with the Cattell-Horn-Carroll model? Some evidence from a joint factor analysis of the Delis-Kaplan Executive Function System and the Woodcock-Johnson III tests of cognitive abilities. *Psychol Sch*. https://doi.org/10.1002/pits.20500
30. Latzman RD, Markon KE (2010): The factor structure and age-related factorial invariance of the Delis-Kaplan Executive Function System (D-KEFS). *Assessment* 17: 172–184.
31. Bollen KA (1989): Structural equations with latent variables. https://doi.org/10.1002/9781118619179
32. Friedman NP, Miyake A, Young SE, DeFries JC, Corley RP, Hewitt JK (2008): Individual differences in executive functions are almost entirely genetic in origin. *J Exp Psychol Gen* 137: 201–225.
33. Karr JE, Hofer SM, Iverson GL, Garcia-Barrera MA (2019): Examining the latent structure of the Delis--Kaplan executive function system. *Arch Clin Neuropsychol* 34: 381–394.
34. Dajani DR, Uddin LQ (2015): Demystifying cognitive flexibility: implications for clinical and developmental neuroscience. *Trends Neurosci* 38: 571–578.
35. Shao Z, Janse E, Visser K, Meyer AS (2014): What do verbal fluency tasks measure? Predictors of verbal fluency performance in older adults. *Front Psychol* 5: 772.

36. Suchy Y, Kraybill ML, Gidley Larson JC (2010): Understanding design fluency: motor and executive contributions. *J Int Neuropsychol Soc* 16: 26–37.
37. Donofry SD, Stillman CM, Erickson KI (2019): A review of the relationship between eating behavior, obesity, and functional brain network organization. *Soc Cogn Affect Neurosci*. https://doi.org/10.1093/scan/nsz085
38. Wijngaarden MA, Veer IM, Rombouts SARB, van Buchem MA, Willems van Dijk K, Pijl H, van der Grond J (2015): Obesity is marked by distinct functional connectivity in brain networks involved in food reward and salience. *Behav Brain Res* 287: 127–134.
39. Geha P, Cecchi G, Todd Constable R, Abdallah C, Small DM (2017): Reorganization of brain connectivity in obesity. *Hum Brain Mapp* 38: 1403–1420.
40. Nummenmaa L, Hirvonen J, Hannukainen JC, Immonen H, Lindroos MM, Salminen P, Nuutila P (2012): Dorsal striatum and its limbic connectivity mediate abnormal anticipatory reward processing in obesity. *PLoS One* 7: e31089.
41. Kullmann S, Pape A-A, Heni M, Ketterer C, Schick F, Häring H-U, *et al.* (2013): Functional network connectivity underlying food processing: disturbed salience and visual processing in overweight and obese adults. *Cereb Cortex* 23: 1247–1256.
42. Kube J, Mathar D, Horstmann A, Kotz SA, Villringer A, Neumann J (2018): Altered monetary loss processing and reinforcement-based learning in individuals with obesity. *Brain Imaging Behav* 12: 1431–1449.
43. Atalayer D, Pantazatos SP, Gibson CD, McOuatt H, Puma L, Astbury NM, Geliebter A (2014): Sexually dimorphic functional connectivity in response to high vs. low energy-dense food cues in obese humans: an fMRI study. *Neuroimage* 100: 405–413.
44. Lips MA, Wijngaarden MA, van der Grond J, van Buchem MA, de Groot GH, Rombouts SARB, *et al.* (2014): Resting-state functional connectivity of brain regions involved in cognitive control, motivation, and reward is enhanced in obese females. *Am J Clin Nutr* 100: 524–531.
45. Sadler JR, Shearrer GE, Burger KS (2018): Body mass variability is represented by distinct functional connectivity patterns. *Neuroimage* 181: 55–63.
46. Uddin LQ, Yeo BTT, Spreng RN (2019): Towards a universal taxonomy of macro-scale functional human brain networks. *Brain Topogr* 32: 926–942.
47. Uddin LQ, Supekar K, Lynch CJ, Cheng KM, Odriozola P, Barth ME, *et al.* (2015): Brain state differentiation and behavioral inflexibility in autism. *Cereb Cortex* 25: 4740–4747.
48. Syan SK, Owens MM, Goodman B, Epstein LH, Meyre D, Sweet LH, MacKillop J (2019): Deficits in executive function and suppression of default mode network in obesity. *Neuroimage Clin* 24: 102015.
49. Menon V (2011): Large-scale brain networks and psychopathology: a unifying triple network model. *Trends Cogn Sci* 15: 483–506.
50. García-García I, Jurado MA, Garolera M, Segura B, Marqués-Iturria I, Pueyo R, *et al.* (2013): Functional connectivity in obesity during reward processing. *NeuroImage* 66: 232–239.
51. Doucet GE, Rasgon N, McEwen BS, Micali N, Frangou S (2018): Elevated body mass index is associated with increased integration and reduced cohesion of sensory-driven and internally guided resting-state functional brain networks. *Cereb Cortex* 28: 988–997.
52. Cohen JI, Yates KF, Duong M, Convit A (2011): Obesity, orbitofrontal structure and function are associated with food choice: a cross-sectional study. *BMJ Open* 1: e000175.
53. Kishinevsky FI, Cox JE, Murdaugh DL, Stoeckel LE, Cook EW 3rd, Weller RE (2012): fMRI reactivity on a delay discounting task predicts weight gain in obese women. *Appetite* 58: 582–592.
54. Maayan L, Hoogendoorn C, Sweat V, Convit A (2011): Disinhibited eating in obese adolescents is associated with orbitofrontal volume reductions and executive dysfunction. *Obesity* 19: 1382–1387.
55. Nomi JS, Vij SG, Dajani DR, Steimke R, Damaraju E, Rachakonda S, *et al.* (2017): Chronnectomic patterns and neural flexibility underlie executive function. *Neuroimage* 147: 861–871.
56. Park B-Y, Moon T, Park H (2018): Dynamic functional connectivity analysis reveals improved association between brain networks and eating behaviors compared to static analysis. *Behav Brain Res* 337: 114–121.
57. Knight SP, Laird E, Williamson W, O'Connor J, Newman L, Carey D, *et al.* (2021): Obesity is associated with reduced cerebral blood flow – modified by physical activity. *Neurobiol Aging* 105: 35–47.
58. Simon AB, Buxton RB (2015): Understanding the dynamic relationship between cerebral blood flow and the BOLD signal: implications for quantitative functional MRI. *Neuroimage* 116: 158–167.
59. Iadecola C (2004): Neurovascular regulation in the normal brain and in Alzheimer's disease. *Nat Rev Neurosci* 5: 347–360.
60. Attwell D, Laughlin SB (2001): An energy budget for signaling in the grey matter of the brain. *J Cereb Blood Flow Metab* 21: 1133–1145.
61. Tak S, Polimeni JR, Wang DJJ, Yan L, Chen JJ (2015): Associations of resting-state fMRI functional connectivity with flow-BOLD coupling and regional vasculature. *Brain Connect* 5: 137–146.
62. Lurie DJ, Kessler D, Bassett DS, Betzel RF, Breakspear M, Kheilholz S, *et al.* (2020): Questions and controversies in the study of time-varying functional connectivity in resting fMRI. *Netw Neurosci* 4: 30–69.
63. Lewis N, Lu H, Liu P, Hou X, Damaraju E, Iraji A, Calhoun V (2020): Static and dynamic functional connectivity analysis of cerebrovascular reactivity: an fMRI study. *Brain Behav* 10: e01516.
64. Kupis L, Goodman ZT, Kircher L, Romero C, Dirks B, Chang C, *et al.* (2021): Altered patterns of brain dynamics linked with body mass index in youth with autism. *Autism Res*. https://doi.org/10.1002/aur.2488
65. Gertel VH, Zhang H, Diaz MT (2020): Stronger right hemisphere functional connectivity supports executive aspects of language in older adults. *Brain Lang* 206: 104771.
66. Nguyen-Rodriguez ST, Chou C-P, Unger JB, Spruijt-Metz D (2008): BMI as a moderator of perceived stress and emotional eating in adolescents. *Eat Behav* 9: 238–246.
67. Abshire DA, Lennie TA, Chung ML, Biddle MJ, Barbosa-Leiker C, Moser DK (2018): Body mass index category moderates the relationship between depressive symptoms and diet quality in overweight and obese rural-dwelling adults. *J Rural Health* 34: 377–387.
68. Baron RM, Kenny DA (1986): The moderator–mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* 51: 1173–1182.
69. Hartanto A, Yong JC, Toh WX (2019): Bidirectional associations between obesity and cognitive function in midlife adults: a longitudinal study. *Nutrients* 11. https://doi.org/10.3390/nu11102343
70. Cunningham GB, Ahn NY (2019): Moderation in sport management research: room for growth. *Meas Phys Educ Exerc Sci* 23: 301–313.
71. Hutchison RM, Morton JB (2015): Tracking the brain's functional coupling dynamics over development. *J Neurosci* 35: 6849–6859.
72. Park DC, Lautenschlager G, Hedden T, Davidson NS, Smith AD, Smith PK (2002): Models of visuospatial and verbal memory across the adult life span. *Psychol Aging* 17: 299–320.
73. Li Y, Gao J, Enkavi AZ, Zaval L, Weber EU, Johnson EJ (2015): Sound credit scores and financial decisions despite cognitive aging. *Proc Natl Acad Sci U S A* 112: 65–69.
74. Samanez-Larkin GR, Knutson B (2015): Decision making in the ageing brain: changes in affective and motivational circuits. *Nat Rev Neurosci* 16: 278–289.
75. Narimani M, Esmaeilzadeh S, Azevedo LB, Moradi A, Heidari B, Kashfi-Moghadam M (2019): Association between weight status and executive function in young adults. *Medicina* 55. https://doi.org/10.3390/medicina55070363
76. Prickett C, Brennan L, Stolwyk R (2015): Examining the relationship between obesity and cognitive function: a systematic literature review. *Obes Res Clin Pract* 9: 93–113.
77. Chang C, Glover GH (2010): Time–frequency dynamics of resting-state brain connectivity measured with fMRI. *Neuroimage* 50: 81–98.
78. Sakoğlu U, Pearlson GD, Kiehl KA, Wang YM, Michael AM, Calhoun VD (2010): A method for evaluating dynamic functional network connectivity and task-modulation: application to schizophrenia. *MAGMA* 23: 351–366.
79. Liu X, Duyn JH (2013): Time-varying functional network information extracted from brief instances of spontaneous brain activity. *Proc Natl Acad Sci U S A* 110: 4392–4397.
80. Jin C, Jia H, Lanka P, Rangaprakash D, Li L, Liu T, *et al.* (2017): Dynamic brain connectivity is a better predictor of PTSD than static connectivity. *Hum Brain Mapp* 38: 4479–4496.
81. Liégeois R, Li J, Kong R, Orban C, Van De Ville D, Ge T, *et al.* (2019): Resting brain dynamics at different timescales capture distinct aspects of human behavior. *Nat Commun* 10: 2317.
82. Liu X, Zhang N, Chang C, Duyn JH (2018): Co-activation patterns in resting-state fMRI signals. *Neuroimage* 180: 485–494.
83. Marshall E, Nomi JS, Dirks B, Romero C, Kupis L, Chang C, Uddin LQ (2020): Co-activation pattern analysis reveals altered salience network dynamics in children with autism spectrum disorder. *Netw Neurosci* 4: 1–16.
84. Kupis L, Romero C, Dirks B, Hoang S, Parlade MV, Beaumont AL, *et al.* (2020): Evoked and intrinsic brain network dynamics in children with autism spectrum disorder. *Neuroimage Clin* 28: 102396.
85. Qiao L, Xu M, Luo X, Zhang L, Li H, Chen A (2020): Flexible adjustment of the effective connectivity between the fronto-parietal and visual regions supports cognitive flexibility. *Neuroimage* 220: 117158.
86. Homack S, Lee D, Riccio CA (2005): Test review: Delis-Kaplan executive function system. *J Clin Exp Neuropsychol* 27: 599–609.
87. Yochim B, Baldo J, Nelson A, Delis DC (2007): D-KEFS Trail Making Test performance in patients with lateral prefrontal cortex lesions. *J Int Neuropsychol Soc* 13: 704–709.
88. Yan C-G, Wang X-D, Zuo X-N, Zang Y-F (2016): DPABI: data processing & analysis for (resting-state) brain imaging. *Neuroinformatics* 14: 339–351.

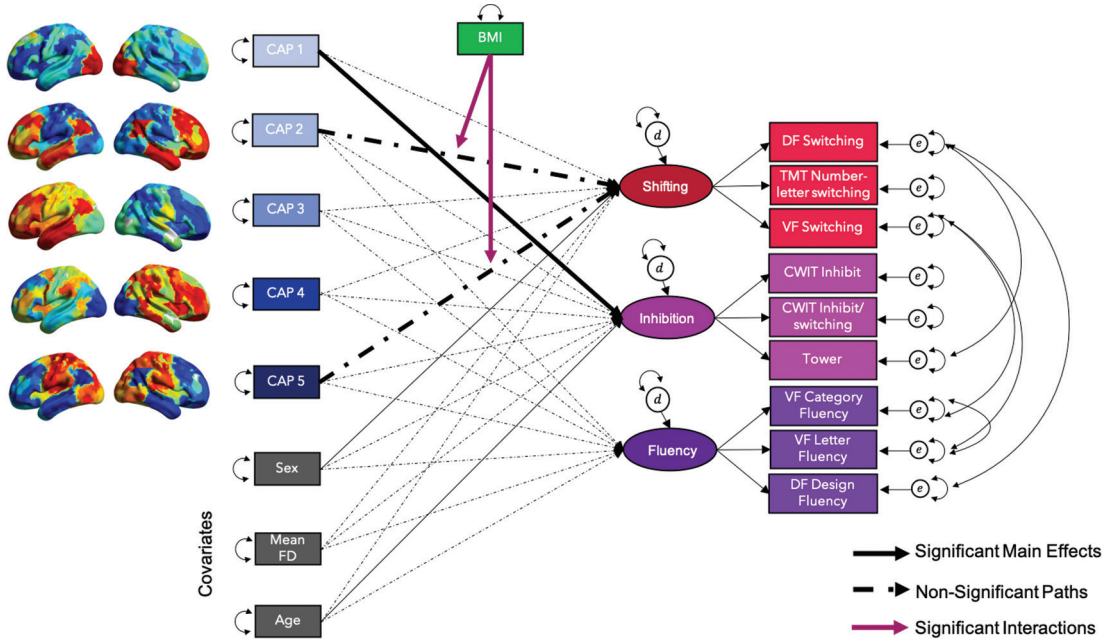
89. Griffanti L, Salimi-Khorshidi G, Beckmann CF, Auerbach EJ, Douaud G, Sexton CE, *et al.* (2014): ICA-based artefact removal and accelerated fMRI acquisition for improved resting state network imaging. *Neuroimage* 95: 232–247.
90. Schaefer A, Kong R, Gordon EM, Laumann TO, Zuo X-N, Holmes AJ, *et al.* (2018): Local-global parcellation of the human cerebral cortex from intrinsic functional connectivity MRI. *Cereb Cortex* 28: 3095–3114.
91. Muthén BO, Muthén LK (2010): IRT in Mplus. Retrieved from www.statmodel.com
92. Muthen LK, Muthen B (2017): *Mplus Version 8 User's Guide.* Los Angeles, CA: Muthen & Muthen.
93. Guàrdia-Olmos J, Peró-Cebollero M, Gudayol-Ferré E (2018): Meta-Analysis of the structural equation models' parameters for the estimation of brain connectivity with fMRI. *Front Behav Neurosci* 12: 19.
94. Beaty RE, Chen Q, Christensen AP, Qiu J, Silvia PJ, Schacter DL (2018): Brain networks of the imaginative mind: dynamic functional connectivity of default and cognitive control networks relates to openness to experience. *Hum Brain Mapp* 39: 811–821.
95. Frazier PA, Tix AP, Barron KE (2004): Testing moderator and mediator effects in counseling psychology research. *J Couns Psychol* 51: 115–134.
96. Iacobucci D, Schneider MJ, Popovich DL, Bakamitsos GA (2016): Mean centering helps alleviate "micro" but not "macro" multicollinearity. *Behav Res Methods* 48: 1308–1317.
97. Kelava A, Werner CS, Schermelleh-Engel K, Moosbrugger H, Zapf D, Ma Y, *et al.* (2011): Advanced nonlinear latent variable modeling: distribution analytic LMS and QML estimators of interaction and quadratic effects. *Struct Equ Model* 18: 465–491.
98. Marsh HW, Hau K-T, Wen Z, Nagengast B, Morin AJS (2013): Moderation. In: Little TD, editor. *The Oxford Handbook of Quantitative Methods: Statistical Analysis*, vol. 2. New York: Oxford University Press, xviii, pp. 361–386.
99. Fairchild AJ, MacKinnon DP (2009): A general model for testing mediation and moderation effects. *Prev Sci* 10: 87–99.
100. Cole DA, Nick EA, Varga G, Smith D, Zelkowitz RL, Ford MA, Lédeczi Á (2019): Are aspects of Twitter use associated with reduced depressive symptoms? The moderating role of in-person social support. *Cyberpsychol Behav Soc Netw* 22: 692–699.
101. Yap MBH, Whittle S, Yücel M, Sheeber L, Pantelis C, Simmons JG, Allen NB (2008): Interaction of parenting experiences and brain structure in the prediction of depressive symptoms in adolescents. *Arch Gen Psychiatry* 65: 1377–1385.
102. Kim J, Zhu W, Chang L, Bentler PM, Ernst T (2007): Unified structural equation modeling approach for the analysis of multisubject, multivariate functional MRI data. *Hum Brain Mapp* 28: 85–93.
103. Beets MW, Foley JT (2008): Association of father involvement and neighborhood quality with kindergartners' physical activity: a multilevel structural equation model. *Am J Health Promot* 22: 195–203.104.
104. Asparouhov T, Muthén B (2009): Exploratory structural equation modeling. *Struct Equ Modeling* 16: 397–438.
105. Miller JW, Stromeyer WR, Schwieterman MA (2013): Extensions of the Johnson-Neyman technique to linear models with curvilinear effects: derivations and analytical tools. *Multivariate Behav Res* 48: 267–300.
106. Karr JE, Hofer SM, Iverson GL (2019): Examining the latent structure of the Delis–Kaplan executive function system. *Arch Clin Neuropsychol*. Retrieved from https://academic.oup.com/acn/article-abstract/34/3/381/4992688
107. Shefer G, Marcus Y, Stern N (2013): Is obesity a brain disease? *Neurosci Biobehav Rev* 37: 2489–2503.
108. García-García I, Jurado MÁ, Garolera M, Segura B, Sala-Llonch R, Marqués-Iturria I, *et al.* (2013): Alterations of the salience network in obesity: a resting-state fMRI study. *Hum Brain Mapp* 34: 2786–2797.
109. Chao S-H, Liao Y-T, Chen VC-H, Li C-J, McIntyre RS, Lee Y, Weng J-C (2018): Correlation between brain circuit segregation and obesity. *Behav Brain Res* 337: 218–227.
110. Alosco ML, Galioto R, Spitznagel MB, Strain G, Devlin M, Cohen R, *et al.* (2013): Cognitive function following bariatric surgery: evidence for improvement 3 years post-surgery. *Am J Surg* 207: 870–876.
111. Prehn K, Jumpertz von Schwartzenberg R, Mai K, Zeitz U, Witte AV, Hampel D, *et al.* (2017): Caloric restriction in older adults—differential effects of weight loss and reduced weight on brain structure and function. *Cereb Cortex* 27: 1765–1778.
112. Frank S, Wilms B, Veit R, Ernst B, Thurnheer M, Kullmann S, *et al.* (2014): Altered brain activity in severely obese women may recover after Roux-en Y gastric bypass surgery. *Int J Obes* 38: 341–348.
113. Coveleskie K, Gupta A, Kilpatrick LA, Mayer ED, Ashe-McNalley C, Stains J, *et al.* (2015): Altered functional connectivity within the central reward network in overweight and obese women. *Nutr Diabetes* 5: e148.
114. Park B-Y, Byeon K, Lee MJ, Chung C-S, Kim S-H, Morys F, *et al.* (2020): Whole-brain functional connectivity correlates of obesity phenotypes. *Hum Brain Mapp*. Retrieved from https://onlinelibrary.wiley.com/doi/abs/10.1002/hbm.25167
115. Avery JA, Powell JN, Breslin FJ, Lepping RJ, Martin LE, Patrician TM, *et al.* (2017): Obesity is associated with altered mid-insula functional connectivity to limbic regions underlying appetitive responses to foods. *J Psychopharmacol* 31: 1475–1484.
116. Contreras-Rodríguez O, Martín-Pérez C, Vilar-López R, Verdejo-Garcia A (2017): Ventral and dorsal striatum networks in obesity: link to food craving and weight gain. *Biol Psychiatry* 81: 789–796.
117. Corbetta M, Shulman GL (2002): Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci* 3: 201–215.
118. Grady CL, Garrett DD (2014): Understanding variability in the BOLD signal and why it matters for aging. *Brain Imaging Behav* 8: 274–283.
119. Kumral D, Şansal F, Cesnaite E, Mahjoory K, Al E, Gaebler M, *et al.* (2020): BOLD and EEG signal variability at rest differently relate to aging in the human brain. *Neuroimage* 207: 116373.
120. Xia Y, Chen Q, Shi L, Li M, Gong W, Chen H, Qiu J (2019): Tracking the dynamic functional connectivity structure of the human brain across the adult lifespan. *Hum Brain Mapp* 40: 717–728.
121. Shine JM, Bissett PG, Bell PT, Koyejo O, Balsters JH, Gorgolewski KJ, *et al.* (2016): The dynamics of functional brain networks: integrated network states during cognitive task performance. *Neuron* 92: 544–554.
122. Baek K, Morris LS, Kundu P, Voon V (2017): Disrupted resting-state brain network properties in obesity: decreased global and putaminal cortico-striatal network efficiency. *Psychol Med* 47: 585–596.
123. Stanley ML, Simpson SL, Dagenbach D, Lyday RG, Burdette JH, Laurienti PJ (2015): Changes in brain network efficiency and working memory performance in aging. *PLoS One* 10: e0123950.
124. Lawrence AJ, Chung AW, Morris RG, Markus HS, Barrick TR (2014): Structural network efficiency is associated with cognitive impairment in small-vessel disease. *Neurology* 83: 304–311.
125. Chén OY, Cao H, Reinen JM, Qian T, Gou J, Phan H, *et al.* (2019): Resting-state brain information flow predicts cognitive flexibility in humans. *Sci Rep* 9: 3879.
126. Bagarinao E, Watanabe H, Maesawa S, Mori D, Hara K, Kawabata K, *et al.* (2019): Reorganization of brain networks and its association with general cognitive performance over the adult lifespan. *Sci Rep* 9: 11352.
127. Hoff GEA-J, Van den Heuvel MP, Benders MJNL, Kersbergen KJ, De Vries LS (2013): On development of functional brain connectivity in the young brain. *Front Hum Neurosci* 7: 650.
128. Xu X, Hanganu-Opatz IL, Bieler M (2020): Cross-Talk of low-level sensory and high-level cognitive processing: development, mechanisms, and relevance for cross-modal abilities of the brain. *Front Neurorobot* 14: 7.
129. Denervaud S, Gentaz E, Matusz PJ, Murray MM (2020): Multisensory gains in simple detection predict global cognition in schoolchildren. *Sci Rep* 10: 1394.
130. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, *et al.* (1996): Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med* 334: 292–295.
131. Enriori PJ, Evans AE, Sinnayah P, Cowley MA (2006): Leptin resistance and obesity. *Obesity* 14 Suppl 5: 254S–258S.
132. Gregor MF, Hotamisligil GS (2011): Inflammatory mechanisms in obesity. *Annu Rev Immunol* 29: 415–445.
133. Nguyen JCD, Killcross AS, Jenkins TA (2014): Obesity and cognitive decline: role of inflammation and vascular changes. *Front Neurosci* 8: 375.
134. Tan ZS, Beiser AS, Fox CS, Au R, Himali JJ, Debette S, *et al.* (2011): Association of metabolic dysregulation with volumetric brain magnetic resonance imaging and cognitive markers of subclinical brain aging in middle-aged adults: the Framingham Offspring Study. *Diabetes Care* 34: 1766–1770.
135. Trollor JN, Smith E, Baune BT, Kochan NA, Campbell L, Samaras K, *et al.* (2010): Systemic inflammation is associated with MCI and its subtypes: the Sydney Memory and Aging Study. *Dement Geriatr Cogn Disord* 30: 569–578.
136. Baune BT, Ponath G, Golledge J, Varga G, Arolt V, Rothermundt M, Berger K (2008): Association between IL-8 cytokine and cognitive performance in an elderly general population—The MEMO-Study. *Neurobiol Aging* 29: 937–944.
137. Raz N, Rodrigue KM (2006): Differential aging of the brain: patterns, cognitive correlates and modifiers. *Neurosci Biobehav Rev* 30: 730–748.
138. Hull JV, Dokovna LB, Jacokes ZJ, Torgerson CM, Irimia A, Van Horn JD, GENDAAR Research Consortium (2018): Corrigendum: resting-state functional connectivity in autism spectrum disorders: a review. *Front Psychiatry* 9: 268.
139. Bos DJ, van Raalten TR, Oranje B, Smits AR, Kobussen NA, van Belle J, *et al.* (2014): Developmental differences in higher-order resting-state networks in Autism Spectrum Disorder. *Neuroimage Clin* 4: 820–827.

140. Cerliani L, Mennes M, Thomas RM, Di Martino A, Thioux M, Keysers C (2015): Increased functional connectivity between subcortical and cortical resting-state networks in Autism Spectrum disorder. *JAMA Psychiatry* 72: 767–777.
141. Ebisch SJH, Gallese V, Willems RM, Mantini D, Groen WB, Romani GL, *et al.* (2011): Altered intrinsic functional connectivity of anterior and posterior insula regions in high-functioning participants with autism spectrum disorder. *Hum Brain Mapp* 32: 1013–1028.
142. Keown CL, Shih P, Nair A, Peterson N, Mulvey ME, Müller R-A (2013): Local functional overconnectivity in posterior brain regions is associated with symptom severity in autism spectrum disorders. *Cell Rep* 5: 567–572.
143. Jacob S, Wolff JJ, Steinbach MS, Doyle CB, Kumar V, Elison JT (2019): Neurodevelopmental heterogeneity and computational approaches for understanding autism. *Transl Psychiatry* 9: 63.
144. Kahathuduwa CN, West BD, Blume J, Dharavath N, Moustaid-Moussa N, Mastergeorge A (2019): The risk of overweight and obesity in children with autism spectrum disorders: a systematic review and meta-analysis. *Obes Rev* 20: 1667–1679.
145. Sedgewick F, Leppanen J, Tchanturia K (2020): Autistic adult outcomes on weight and body mass index: a large-scale online study. *Eat Weight Disord* 25: 795–801.
146. Pedhazur EJ (1997): *Multiple Regression in Behavioral Research: Explanation and Prediction*. New York: Harcourt Brace College Publishers.
147. Berg EA (1948): A simple objective technique for measuring flexibility in thinking. *J Gen Psychol* 39: 15–22.
148. Allen EA, Damaraju E, Plis SM, Erhardt EB, Eichele T, Calhoun VD (2014): Tracking whole-brain connectivity dynamics in the resting state. *Cereb Cortex* 24: 663–676.
149. Nilsson L-G, Nilsson E (2009): Overweight and cognition. *Scand J Psychol* 50: 660–667.
150. Childers DK, Allison DB (2010): The "obesity paradox": a parsimonious explanation for relations among obesity, mortality rate and aging? *Int J Obes* 34: 1231–1238.
151. Cole DA, Maxwell SE (2003): Testing mediational models with longitudinal data: questions and tips in the use of structural equation modeling. *J Abnorm Psychol* 112: 558–577.
152. Maxwell SE, Cole DA (2007): Bias in cross-sectional analyses of longitudinal mediation. *Psychol Methods* 12: 23–44.
153. Maxwell SE, Cole DA, Mitchell MA (2011): Bias in cross-sectional analyses of longitudinal mediation: partial and complete mediation under an autoregressive model. *Multivariate Behav Res* 46: 816–841.
154. American Psychopathological Association. Meeting (2011): *Causality and Psychopathology: Finding the Determinants of Disorders and Their Cures*. New York: Oxford University Press.
155. Shrout PE (2011): Commentary: mediation analysis, causal process, and cross-sectional data. *Multivariate Behav Res* 46: 852–860.
156. Bischof GN, Park DC (2015): Obesity and aging: consequences for cognition, brain structure, and brain function. *Psychosom Med* 77: 697–709.
157. Laurent JS, Watts R, Adise S, Allgaier N, Chaarani B, Garavan H, *et al.* (2020): Associations among body mass index, cortical thickness, and executive function in children. *JAMA Pediatr* 174: 170–177.
158. Shields GS, Moons WG, Slavich GM (2017): Inflammation, Self-regulation, and health: an Immunologic model of self-regulatory failure. *Perspect Psychol Sci* 12: 588–612.
159. Raemaekers M, Schellekens W, Petridou N, Ramsey NF (2018): Knowing left from right: asymmetric functional connectivity during resting state. *Brain Struct Funct* 223: 1909–1922.
160. Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, *et al.* (2009): Correspondence of the brain's functional architecture during activation and rest. *Proc Natl Acad Sci U S A* 106: 13040–13045.
161. Nomi JS, Uddin LQ (2015): Developmental changes in large-scale network connectivity in autism. *Neuroimage Clin* 7: 732–741.
162. Agcaoglu O, Miller R, Mayer AR, Hugdahl K, Calhoun VD (2015): Lateralization of resting state networks and relationship to age and gender. *Neuroimage* 104: 310–325.
163. Murphy K, Fox MD (2017): Towards a consensus regarding global signal regression for resting state functional connectivity MRI. *Neuroimage* 154: 169–173.
164. Ciric R, Rosen AFG, Erus G, Cieslak M, Adebimpe A, Cook PA, *et al.* (2018): Mitigating head motion artifact in functional connectivity MRI. *Nat Protoc* 13: 2801–2826.
165. Power JD, Plitt M, Laumann TO, Martin A (2017): Sources and implications of whole-brain fMRI signals in humans. *Neuroimage* 146: 609–625.
166. Hyder F, Rothman DL (2010, June 15): Neuronal correlate of BOLD signal fluctuations at rest: err on the side of the baseline. *Proc Natl Acad Sc U S A* 107: 10773–10774.
167. Schölvinck ML, Maier A, Ye FQ, Duyn JH, Leopold DA (2010): Neural basis of global resting-state fMRI activity. *Proc Natl Acad Sci U S A* 107: 10238–10243.
168. Wang J, Wang X (2019): *Structural Equation Modeling: Applications Using Mplus*. Hoboken, NJ: John Wiley & Sons.
169. Sardeshmukh SR, Vandenberg RJ (2017): Integrating moderation and mediation: a structural equation modeling approach. *Organ Res Methods* 20: 721–745.

LAY SUMMARY

Being overweight or obese is a major public health concern and impacts not just physical health symptoms but also cognitive functioning and brain structure and function. However, little is known about how weight or body mass index (BMI) impacts the relationship between brain dynamics, or time-varying brain network activation patterns, and executive function in the domains of inhibition, shifting, and fluency. Using co-activation pattern analysis, a method to examine time-varying relationships among brain networks, and structural equation modeling, we identified various brain states that were moderated by BMI when predicting shifting. Our findings provide novel information showing that the relationship between various co-activation patterns and cognitive flexibility depends on BMI. Our results suggest that this relationship is specifically altered in overweight/obese individuals and that BMI should be considered when studying relationships between brain network dynamics and executive function.

GRAPHICAL ABSTRACT



Supplementary Materials

Global Signal. Preprocessing was additionally conducted without global mean signal regression. The same analysis steps were taken to obtain the optimal *k*-value as done with global mean signal regression, resulting in five co-activation patterns (CAPs) (**Figure S5**). The resulting CAPs revealed the influence of the global signal, notably in CAPs 3 and 5. CAP 3 shows all nodes with activity, and CAP 5 shows all nodes with inactivity representing the global signal across all nodes. Thus, this CAP analysis without global mean signal regression shows that when the global signal has a noticeable influence on a dynamic CAP analysis, it presents as network nodes in some CAPs being all active or inactive. Further, a comparison of the whole-brain activation patterns further revealed the necessity to regress out the global signal in this dataset (**Figure S6**). Further, prior work suggests that whether or not the removal of the signal through GSR is good or bad depends on the scientific question and should be considered when interpreting the results (163). Additionally, the removal of the global signal as a preprocessing step significantly mitigates artifacts from a variety of sources (164,165). Although in some cases the global signal can represent neuronal signal (166,167), taking the above position, in this case removal of the global signal, was beneficial to obtain CAPs associated with cognition.

Tests of Assumptions. The data were screened for outliers, missingness in data, and tests of assumptions. Outliers were identified in BMI; however, the values represented physiologically obtainable values so they were retained. The average percentage of missing data was .1%. The assumptions of normality, linearity, and homogeneity were assessed using SPSS, and they were not violated (**Figure S7**). Further, the main results from the study were tested without BMI outliers, and six subjects were removed.

Interactions. First, the significant interactions between BMI and CAP 2 (characterized by co-activation among the L-FPN, M-FPN, and limbic nodes) dwell time (DT) were still present while predicting shifting, $b = 0.06$, $SE = 0.03$, 95% confidence interval (CI) [0.01, 0.11], but not inhibition, $b = -0.06$, $SE = 0.04$, 95% CI [−0.13, 0.012]. There were also still significant interactions between BMI and CAP 5 (characterized by co-activation among the DAN, M-CIN, somatosensory motor, and visual network nodes) DT predicting shifting, $b = 0.07$, $SE = 0.03$, 95% CI [0.02, 0.12].

Main Effects. There was additionally a main effect still present for DT of CAP 1 (characterized by co-activation among the visual network) predicting inhibition, $b = -0.88$, $SE = 0.42$, 95% CI [−1.71, −0.04].

Bootstrapping. The main results in the manuscript were additionally reanalyzed using bootstrapping with 5000 bootstrap samples in Mplus (92,168) as previously recommended for interaction models with latent variables (169). The bootstrap CIs were reported for each result.

Interactions. After bootstrapping, the significant interactions between BMI and CAP 2 (characterized by co-activation among the L-FPN, M-FPN, and limbic nodes) DT was still present while predicting shifting, $b = 0.05$, $SE = 0.03$, 95% CI [0.004, 0.11], but not inhibition, $b = -0.07$, $SE = 0.03$, 95% CI [−0.13, 0.0104]. There were also still significant interactions between BMI and CAP 5 (characterized by co-activation among the DAN, M-CIN, somatosensory motor, and visual network nodes) DT predicting shifting, $b = 0.06$, $SE = 0.03$, 95% CI [0.01, 0.11].

Main Effects. There was additionally still a main effect for DT of CAP 1 (characterized by co-activation among the visual network) predicting inhibition, $b = -0.90$, $SE = 0.43$, 95% CI [−1.78, −0.05].

Every variable was tested for assumptions of normality, homogeneity, and linearity. Independence was not a concern, as the data were cross-sectional. Two variables are presented for the test of normality, and all variables met the normality assumption. Next, every dependent variable met the assumptions of homogeneity and linearity.

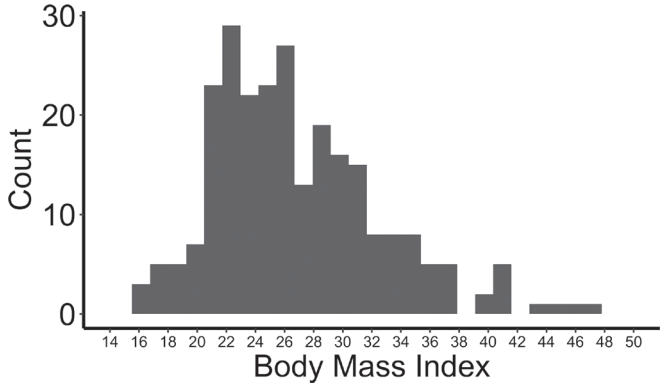


Fig. S1. Distribution of body mass index.

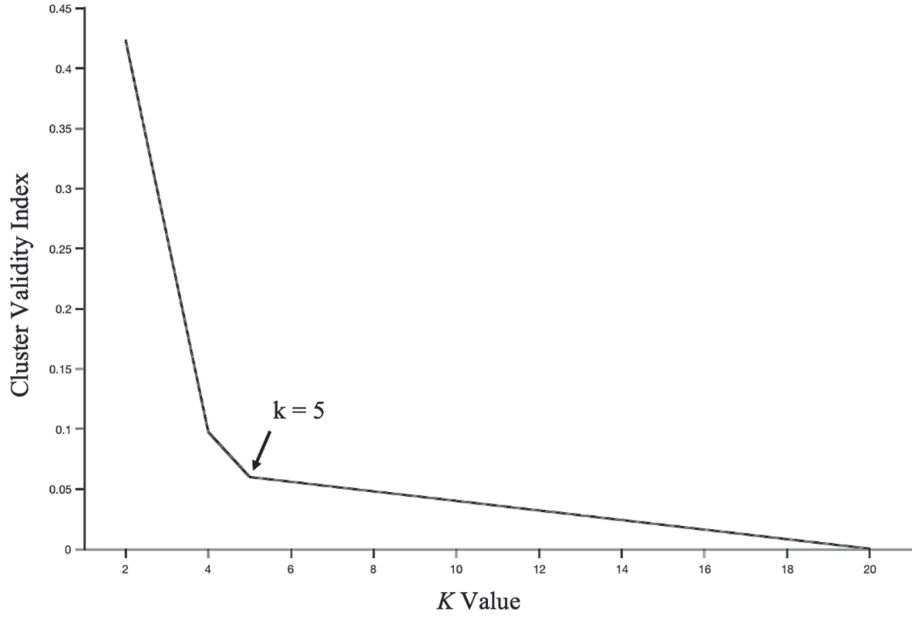


Fig. S2. **Elbow criterion.** The elbow criterion identifies k = 5 clusters.

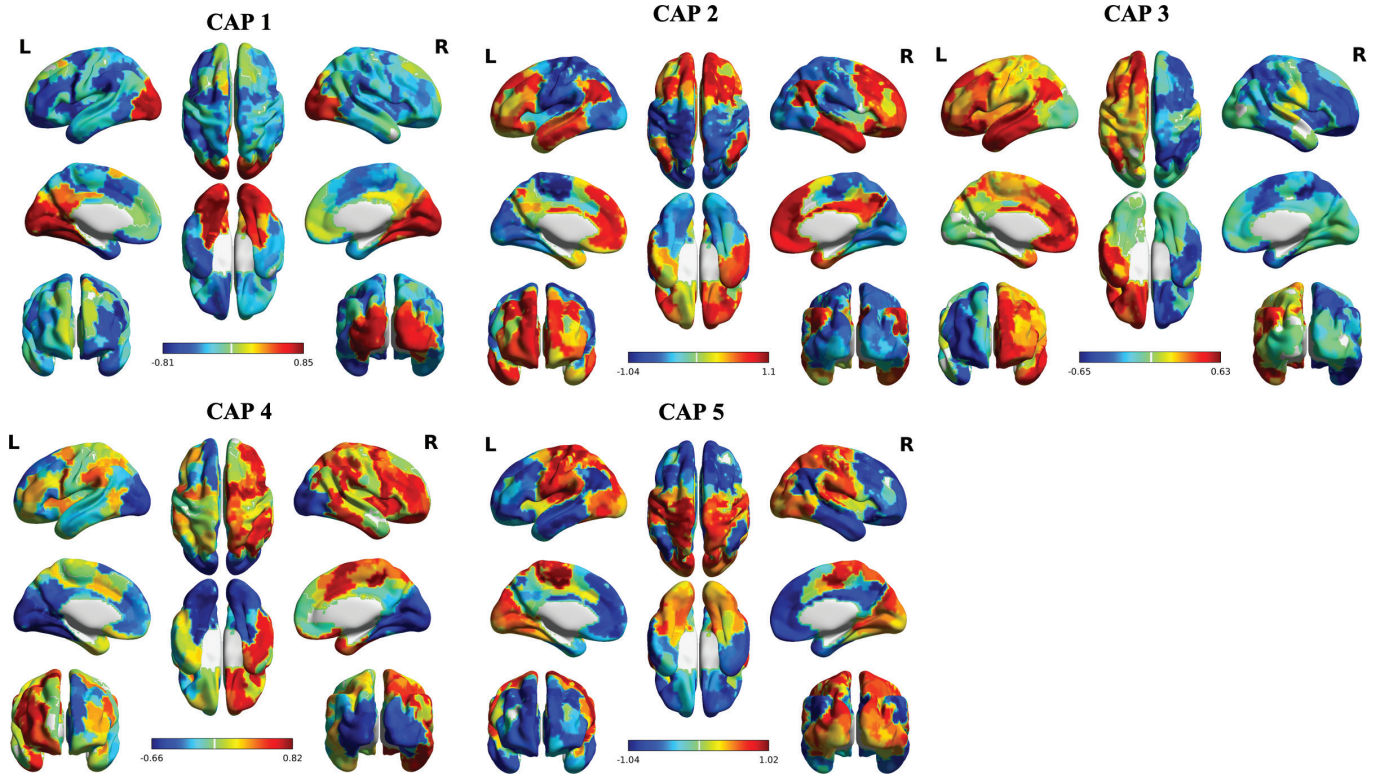


Fig. S3. **Co-activation patterns.** CAP 1 was characterized by co-activation among the visual network. CAP 2 was characterized by co-activation among the L-FPN, M-FPN, and limbic nodes. CAP 3 was characterized by co-activation among the M-FPN. CAP 4 was characterized by co-activation among the L-FPN, DAN, limbic, and M-CIN nodes. Lastly, CAP 5 was characterized by co-activation among the dorsal frontoparietal (D-FPN), M-CIN, somatosensory motor, and visual network nodes.

Table S1. **Summary of Two-Factor Measurement Models**

Model	χ^2 (df)	*P*	CFI	SRMR	RMSEA
1. Shifting/inhibition and fluency	37.29 (21)	.016	.97	.04	.06
2. Shifting/fluency and inhibition	25.18 (21)	.240*	.99	.03	.03
3. Inhibition/fluency and shifting	44.65 (21)	.002	.96	.05	.07

* $p > .05$.

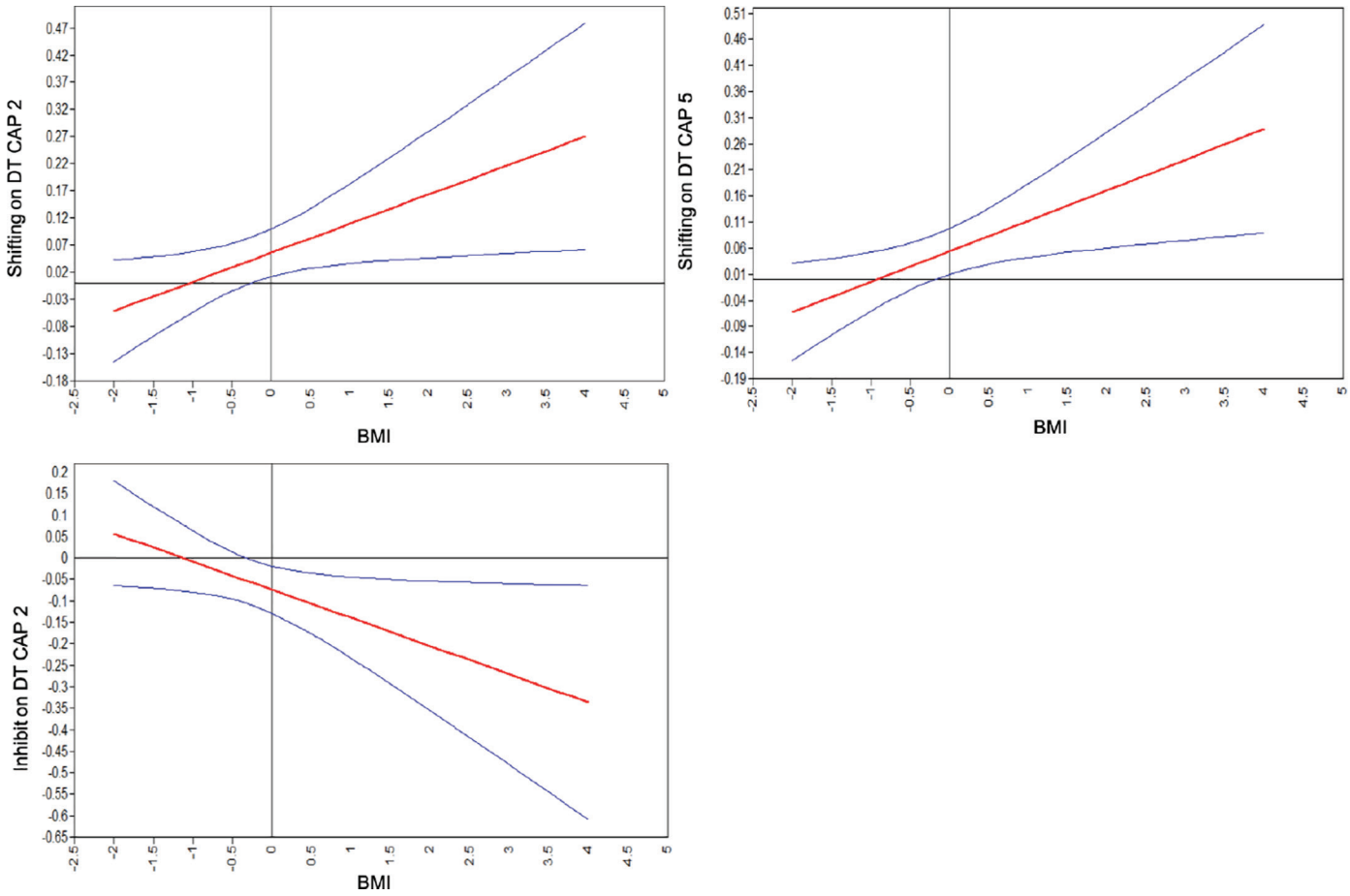


Fig. S4. Johnson-Neyman plots.

Table S2. Summary of Simple Slopes Analysis

Unstandardized	*b*	*SE*
Shifting		
BMI × DT CAP 2 (−1 SD)	−.04	.15
BMI × DT CAP 2 (+1 SD)	.06	.15
BMI × DT CAP 2 (−2 SD)	−.10	.15
BMI × DT CAP 2 (+2 SD)	.11	.15
BMI × DT CAP 2 (−3 SD)	−.16	.16
BMI × DT CAP 2 (+ 3 SD)	.17	.16
BMI × DT CAP 5 (−1 SD)	−.13	.15
BMI × DT CAP 5 (+1 SD)	−.02	.14
BMI × DT CAP 5 (−2 SD)	−.19	.16
BMI × DT CAP 5 (+2 SD)	.04	.15
BMI × DT CAP 5 (−3 SD)	−.25	.17
BMI × DT CAP 5 (+ 3 SD)	.10	.15
BMI × Transitions (−1 SD)	.01	.01
BMI × Transitions (+1 SD)	.001	.01
BMI × Transitions (−2 SD)	.01	.01
BMI × Transitions (+2 SD)	−.002	.01
BMI × Transitions (−3 SD)	.01	.01
BMI × Transitions (+3 SD)	−.01	.01
Inhibition		
BMI × DT CAP 2 (−1 SD)	.20	.19
BMI × DT CAP 2 (+1 SD)	.07	.20
BMI × DT CAP 2 (−2 SD)	.27	.20
BMI × DT CAP 2 (+2 SD)	.01	.21
BMI × DT CAP 2 (−3 SD)	.34	.21
BMI × DT CAP 2 (+ 3 SD)	−.06	.22
BMI × DT CAP 5 (−1 SD)	.10	.19
BMI × DT CAP 5 (+1 SD)	−.01	.18
BMI × DT CAP 5 (−2 SD)	.04	.18
BMI × DT CAP 5 (+2 SD)	−.07	.19
BMI × DT CAP 5 (−3 SD)	.21	.21
BMI × DT CAP 5 (+ 3 SD)	−.12	.20
Fluency		
BMI × DT CAP 4 (−1 SD)	−.15	.19
BMI × DT CAP 4 (+1 SD)	−.05	.18
BMI × DT CAP 4 (−2 SD)	−.26	.21
BMI × DT CAP 4 (+2 SD)	.05	.19
BMI × DT CAP 4 (−3 SD)	−.26	.21
BMI × DT CAP 4 (+ 3 SD)	.05	.19

*$p < .05$. **$p < .01$. ***$p < .001$.

Table S3. Frequency of Occurrence of Each Co-activation Pattern (CAP)

	Percentage % (*SD*)
CAP 1	19.36 (.04)
CAP 2	19.29 (.04)
CAP 3	18.60 (.04)
CAP 4	23.39 (.04)
CAP 5	19.35 (.04)

Table S4. Summary of Main Effects. Only variables of interest were included within the table; however, covariates included age, sex, and head motion.

	β	*B*	*SE*	95% CI [lower 2.5%, upper 2.5%]
Shift				
DT CAP 1	−.04	−.11	.18	[−.45, .24]
DT CAP 3	.06	.17	.17	[−.17, .51]
DT CAP 4	−.02	−.06	.17	[−.39, .26]
F CAP 1	−.08	−3.90	2.77	[−9.33, 1.53]
F CAP 2	−.002	−.12	2.82	[−5.65, 5.41]
F CAP 3	.06	2.97	3.00	[−2.90, 8.85]
F CAP 4	.002	.13	2.86	[−5.48, 5.73]
F CAP 5	.03	1.46	2.89	[−4.20, 7.12]
BMI	.13	.04	.02	[.001, .09]
Age	−.07	−.02	.02	[−.05,.01]
Mean FD	−.04	−.95	1.49	[−3.86, 1.96]
Sex	.18	.72	.23	[.28, 1.16]
Inhibition				
DT CAP 1	−.24	−.83	.41	[−1.64, −.02]
DT CAP 3	−.06	−.24	.43	[−1.08, .61]
DT CAP 4	−.03	−.09	.44	[−.94, .77]
DT CAP 5	−.03	−.09	.37	[−.81, .63]
F CAP 1	.01	−.54	3.52	[−6.36, 7.44]
F CAP 2	−.01	−.73	3.66	[−7.91, 6.45]
F CAP 3	−.03	−1.82	3.92	[−9.50, 5.87]
F CAP 4	.05	3.44	3.65	[−3.71, 10.59]
F CAP 5	−.03	−1.69	3.63	[−8.80, 5.41]
Transitions	− 17	−.04	.04	[−.11, .03]
BMI	−.15	−.06	.03	[−.12, −.01]
Age	.14	.05	.02	[.01, .08]
Mean FD	−.03	−.73	1.89	[−4.43, 2.97]
Sex	−.07	−.35	.28	[.01, .08]
Fluency				
DT CAP 1	.003	.01	.36	[−.70, .71]
DT CAP 2	−.13	−.30	.28	[−.86, .25]
DT CAP 3	.03	.08	.39	[−.69, .84]
DT CAP 4	−21	−.51	.29	[−.51, .10]
DT CAP 5	−05	−.13	.33	[−.77, .52]
F CAP 1	−.01	−.23	3.16	[−6.43, 5.96]
F CAP 2	.09	4.24	3.25	[−2.12, 10.60]
F CAP 3	−.09	−4.59	3.58	[−11.61, 2.43]
F CAP 4	−.04	−2.07	3.24	[−8.42, 4.27]
F CAP 5	.03	1.52	3.30	[−4.96, 7.99]
Transitions	−.13	−.02	.04	[−.10, .05]
BMI	.01	.004	.03	[−.05, .05]
Age	−.02	−.01	.02	[−.04, .03]
Mean FD	.02	.36	1.71	[−2.99, 3.70]
Sex	−.06	0–.22	.26	[−.73, .28]

CI, confidence interval; DT, dwell time; F, frequency; BMI, body mass index; Mean FD, mean framewise displacement.

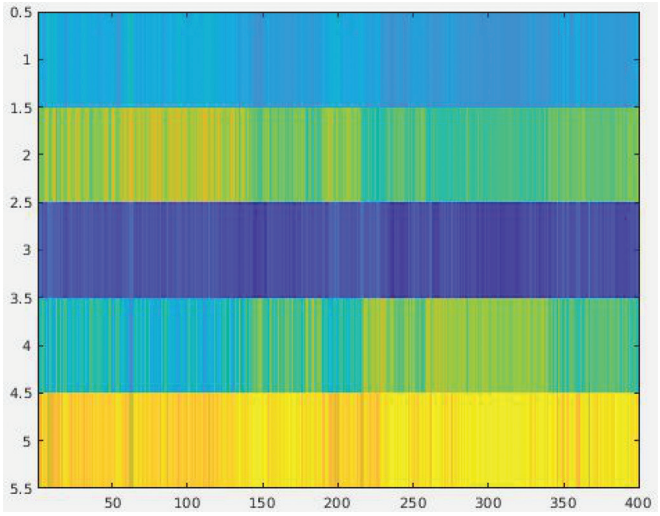


Fig. S5. Co-activation pattern without global signal regression.

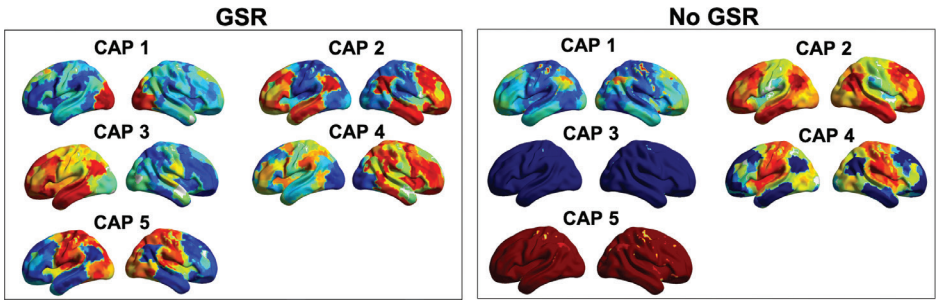


Fig. S6. Co-activation patterns with global signal regression (GSR) and without global signal regression.

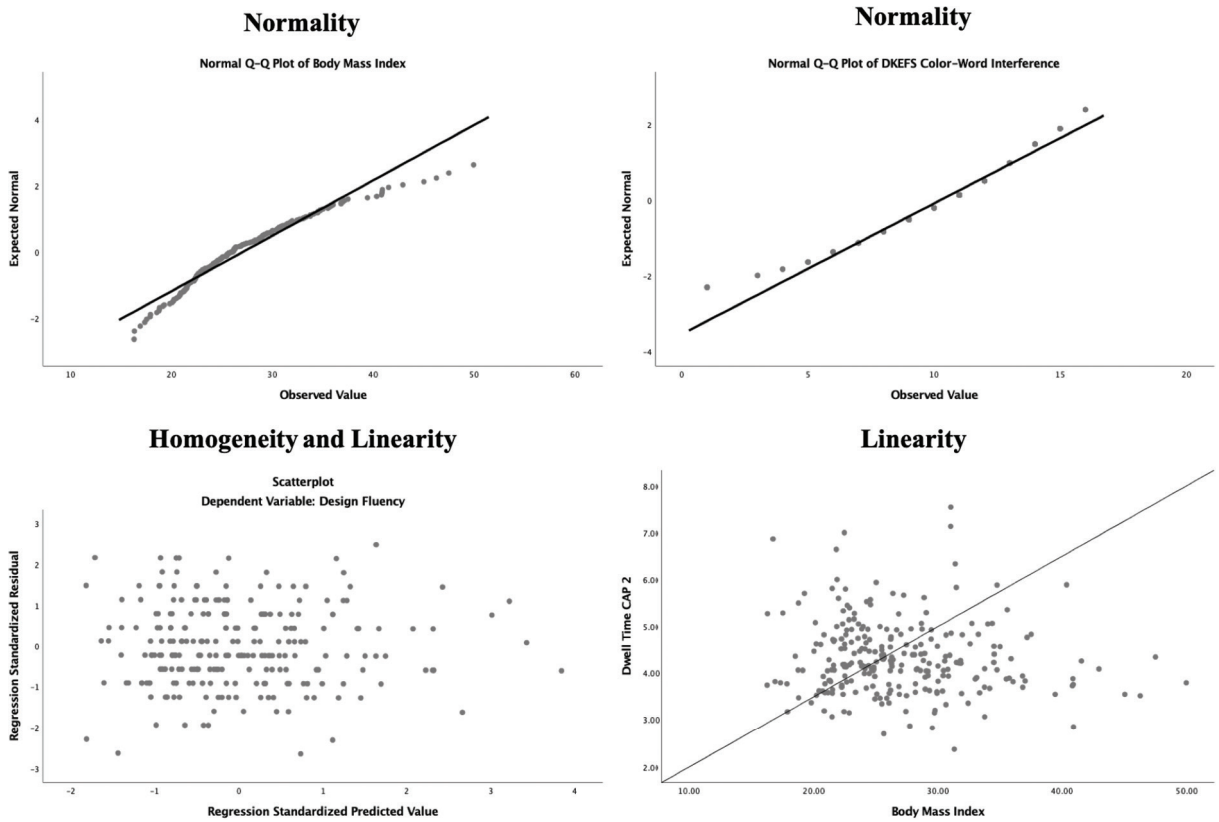


Fig. S7. Tests of assumptions.

