

Body mass index moderates brain dynamics and executive function: A structural equation modeling approach

Running title: Body mass index impacts on brain dynamics and executive function

Lauren Kupis¹, Zachary T. Goodman¹, Salome Kornfeld¹, Celia Romero¹, Bryce Dirks¹, Leigha

Kircher¹, Catie Chang^{2,3,4}, Maria M. Llabre¹, Jason S. Nomi¹, Lucina Q. Uddin^{1,5*}

¹Department of Psychology, University of Miami, Coral Gables FL, USA

²Department of Electrical Engineering and Computer Science, Vanderbilt University, Nashville, TN, USA

³Department of Biomedical Engineering, Vanderbilt University, Nashville, TN, USA

⁴Vanderbilt University Institute of Imaging Science, Vanderbilt University, Nashville, TN, USA

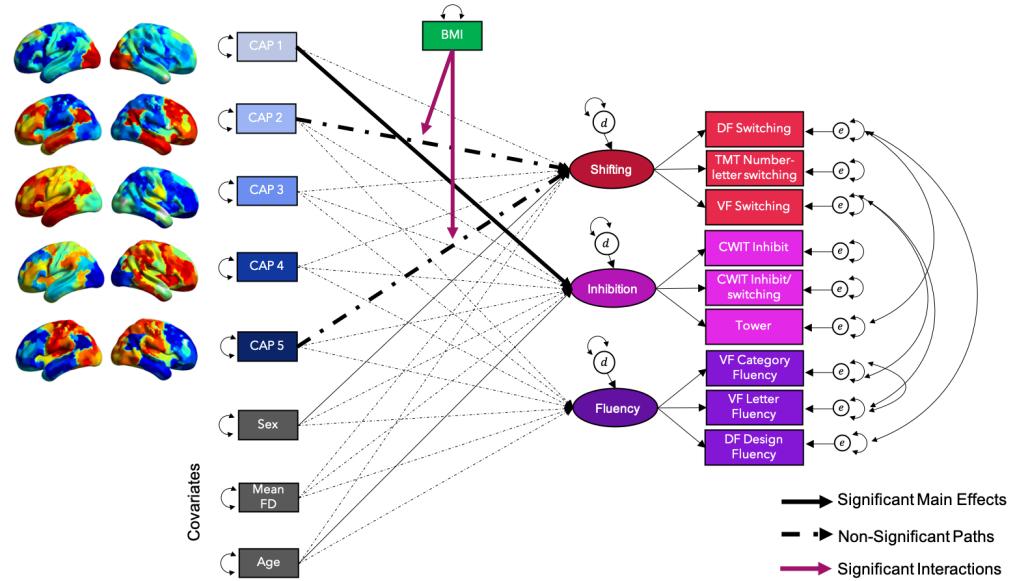
⁵Neuroscience Program, University of Miami Miller School of Medicine, Miami, FL, USA

*Correspondence should be addressed to:

Lauren Kupis
University of Miami
P.O. Box 248185-0751
Coral Gables, FL 33124
Email: lbk48@miami.edu
Phone: 305-284-3265

*Submitting to Aperture (does not say there is a word limit for science articles, only review articles)

Graphical Abstract



Abstract (350 word limit, at 400)

Background

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 $26.95 \text{ kg/m}^2 \pm 5.90 \text{ SD}$) 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

analysis (CAP). 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 with non-significant interactions were assessed for 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. In all significant models, 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.

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 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.

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 being 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 in later-life (12) and brain atrophy (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: 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 provides 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 provide 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 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 suggests 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, was 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 affected by an individual's BMI.

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 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 are affected by varying levels of BMI (68).

In the current study, BMI was tested as a moderator primarily due to: 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., submitted). 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).

The current 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. Examination of the dynamic interactions among the M-CIN, L-FPN, and M-FPN have provided important information about the network interactions subserving cognition, however, large-scale network interactions with other brain regions, such as the visual network, also lends 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

The current 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 1) available neuroimaging and behavioral data 2) no current DSM diagnosis 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.

Table 1

	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.

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 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 Delis-Kaplan Executive Function System (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 task (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 a 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: TR = 1400 ms, 2 x 2 x 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 FSL and SPM-12 (<https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>), and were as follows: removal of the first 5 volumes to allow scanner signal to reach equilibrium, despiking, realignment, normalization directly to the 3 mm MNI template, and smoothing (6 mm 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 resting-state fMRI 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 the **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 (CAP) Analysis

The time series were extracted from the 400 nodes for each subject and were converted to z-statistics and concatenated into one (nodes x timepoints) matrix (where the number of timepoints is 399 TR x 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 $k = 2\text{-}20$ 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 5 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 the resting-state fMRI 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, then a structural moderated model was examined. Confirmatory factor analysis (measurement model) and structural equation modeling (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 are publicly available (https://github.com/lkupis/NKI_BMI). Covariates included mean FD, age, and sex. All

models were assessed for goodness of fit by examining: 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** and the final model is presented in **Figure 4**.

Figure 1

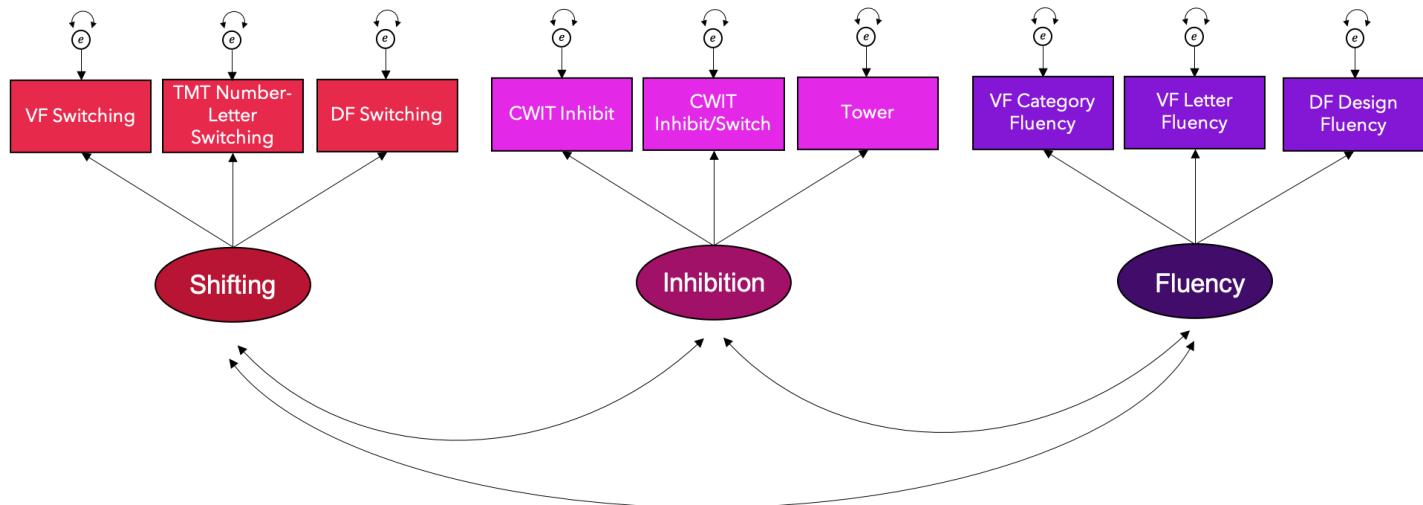


Figure 1. Confirmatory Factor Analysis

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

Structural Model

The best fitting model from the confirmatory factor analysis was tested within the framework of structural equation modeling (SEM). The latent variable(s) in the model were the dependent variables in the SEMs. The use of structural equation models have 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 5 CAPs and the latent variable (shifting, inhibition, or fluency). 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 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 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 previously done (64,100,101), only variables within non-significant interactions were tested for main effects as these variables were not dependent on BMI. Covariates included mean FD, age, and sex as previously done in SEM (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 re-computed without BMI outliers and with bootstrapping. The outlier and bootstrapping analyses can be found in the **Supplementary Materials**. To minimize type II error when performing a moderation in SEM, an alpha 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).

Figure 2

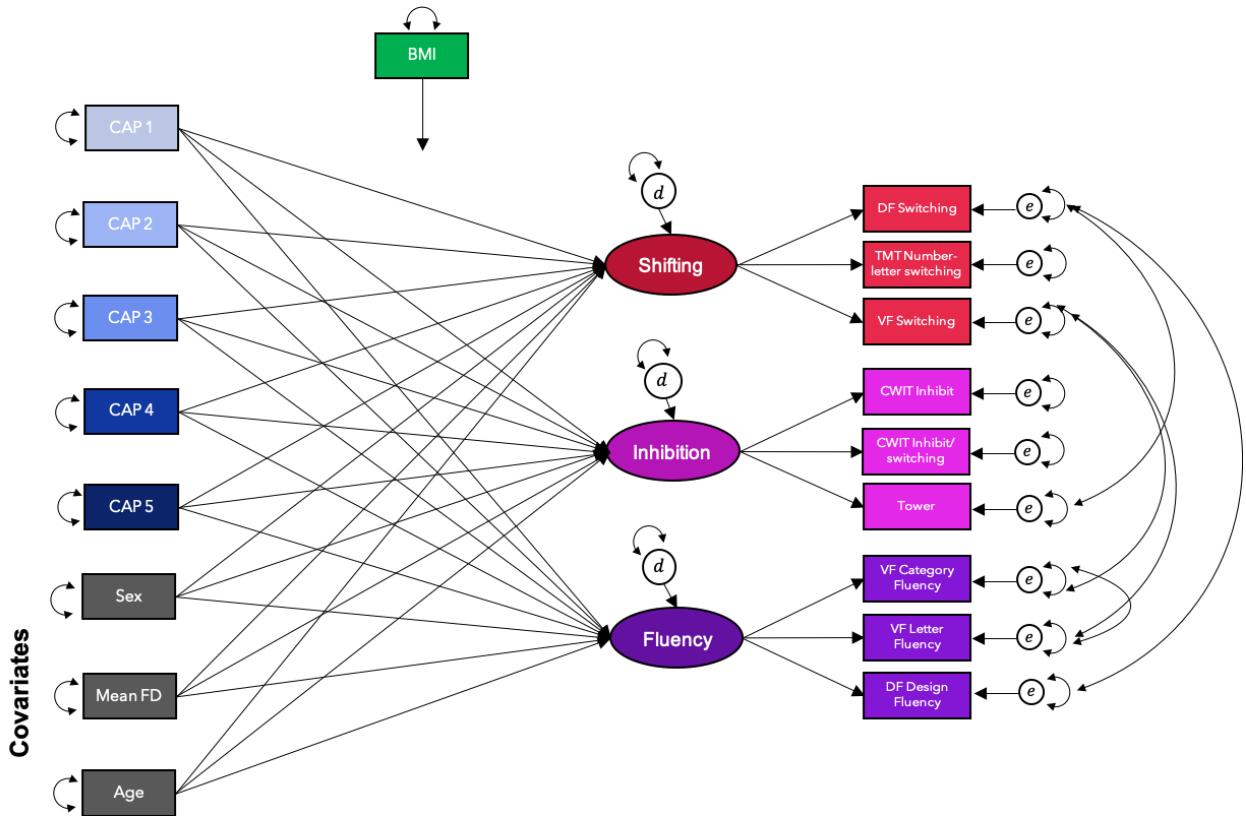


Figure 2. Structural Equation Model

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

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

dorsal frontoparietal (D-FPN), M-CIN, somatosensory motor, and visual network nodes. See a graphical presentation of the CAPs in **Figure S3**; 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/>).

Figure 3

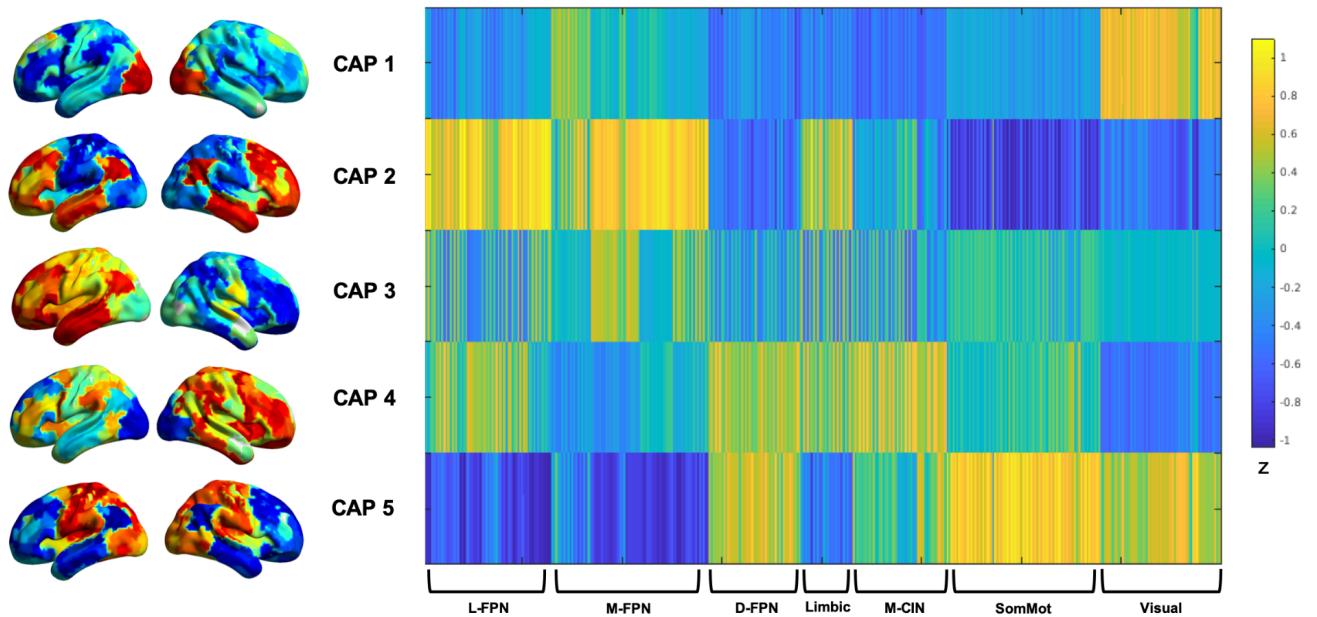


Figure 3. Recurring co-activation patterns

Co-activation patterns (CAPs) showing brain regions 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 apriori three-factor model (33).

The three-factor model included three latent factors of shift, inhibition, and fluency, and each factor 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 loading 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 results of the three-factor measurement model.

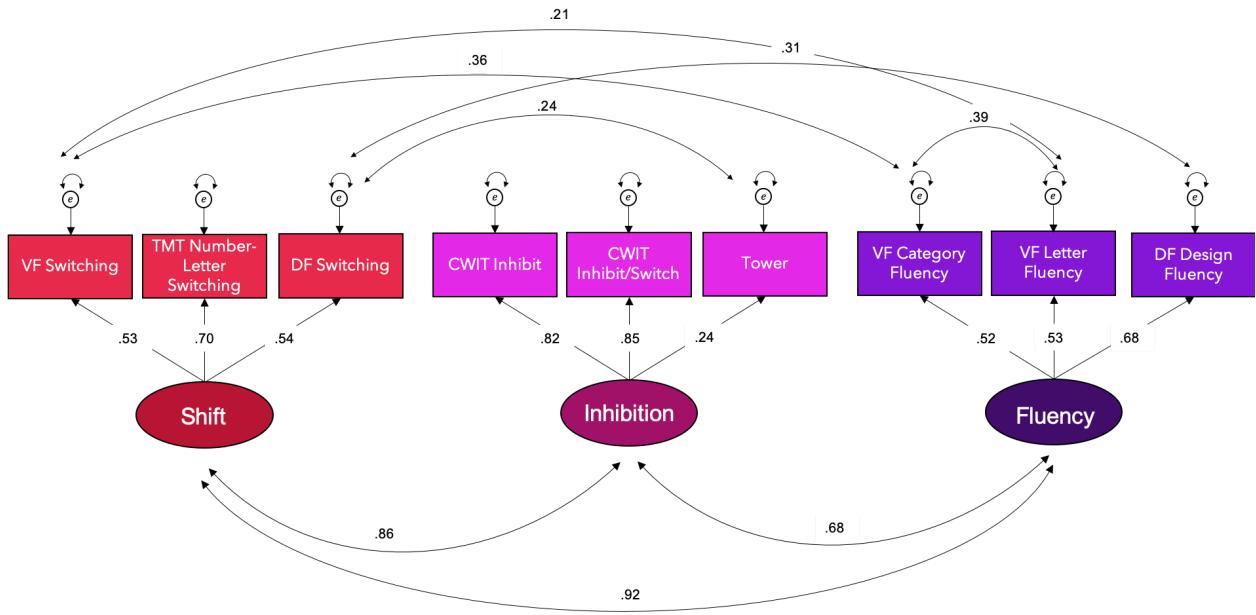
The three-factor variables were significantly correlated with each other (p 's $< .001$; See **Figure 4**). Examination of the estimates of the correlations between pairs of residuals revealed various significant correlations (p 's $< .01$; **Figure 4**). Previous work suggests different EFs are correlated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

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	0.00		[1.00, 1.00]
2. DF Switch	.54	0.80	.12	< 0.001***	[0.57, 1.02]
3. VF Switch	.53	0.95	.14	< 0.001***	[0.68, 1.22]
Inhibition					
1. CWIT Inhibition	.85	1.00	0.00		[1.00, 1.00]
2. CWIT Inhibition/Switch	.82	1.01	.09	< 0.001***	[0.84, 1.18]
3. Tower	.24	0.23	.07	< 0.001***	[0.09, 0.36]
Fluency					
1. VF Letter	.53	1.00	0.00		[1.00, 1.00]
2. VF Category	.52	1.02	.16	< 0.001***	[0.71, 1.33]
3. DF Fluency	.68	1.00	.18	< 0.001***	[0.65, 1.35]

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

Figure 4



$$\chi^2 = 18.68 \text{ (df} = 19, p = .477\text{)}, \text{ CFI} = 1.00, \text{ SRMR} = .03, \text{ and RMSEA} = < .001$$

Figure 4. Final three-factor measurement model

VF, Verbal Fluency; TMT; Trail Making Test; DF, Design Fluency; CWIT, Color-Word Interference Test.

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.

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, $b = 0.05, SE = 0.03, p = .029, 95\% \text{ CI } [0.01, 0.23]$, and inhibition, $b = -0.07, SE = 0.03, p = .041, 95\% \text{ CI } [-0.13, -0.003]$.

There were also a significant interaction between BMI and CAP 5 (characterized by co-activation among the DAN, M-CIN, somatosensory motor, and visual network nodes) DT predicting shifting, $b = 0.06$, $SE = 0.02$, $p = .013$, 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 significant interactions were re-analyzed without BMI outliers and with bootstrapping and only significant interactions with shifting remained (see **Supplementary Materials**).

The significant 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 significant BMI x CAP DT interactions predicting shifting and inhibition, significance was reached at average and high levels of BMI (0 to 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 dynamics and executive functioning.

Table 3. Summary of Interactions

<i>Unstandardized</i>	β	<i>b</i>	<i>SE</i>	<i>p</i>	95% CI	R^2
[lower 2.5%, upper 2.5%]						
Shifting						
BMI x DT CAP 1	-.05	-0.03	0.03	.327	[-0.09, 0.03]	.05
BMI x DT CAP 2	.12	0.05	0.03	.029*	[0.01, 0.23]	.06
BMI x DT CAP 3	-.05	-0.03	0.03	.320	[-0.08, 0.03]	.05

BMI x DT CAP 4	.05	0.02	0.02	.412	[-0.03, 0.07]	.05
BMI x DT CAP 5	.14	0.06	0.02	.013*	[0.01, 0.11]	.06
BMI x F CAP 1	-.04	-0.35	0.50	.481	[-1.34, 0.63]	.05
BMI x F CAP 2	.08	0.67	0.47	.149	[-0.24, 1.59]	.05
BMI x F CAP 3	-.09	-0.74	0.45	.100	[-1.62, 0.14]	.04
BMI x F CAP 4	.01	0.11	0.50	.832	[-0.88, 1.09]	.04
BMI x F CAP 5	.05	0.43	0.48	.376	[-0.52, 1.37]	.05
BMI X Transitions	-.09	-0.003	0.002	.099	[-0.01, 0.001]	.05

Inhibition

BMI x DT CAP 1	-.001	-0.001	0.04	.988	[-0.08, 0.07]	.04
BMI x DT CAP 2	-.12	-0.07	0.03	.041*	[-0.13, -0.003]	.05
BMI x DT CAP 3	.08	0.05	0.03	.157	[-0.02, 0.12]	.04
BMI x DT CAP 4	-.03	-0.02	0.03	.562	[-0.08, 0.04]	.04
BMI x DT CAP 5	-.11	-0.06	0.03	.063	[-0.11, 0.003]	.05
BMI x F CAP 1	.06	0.72	0.64	.256	[-0.53, 1.97]	.04
BMI x F CAP 2	-.09	-0.89	0.59	.126	[-0.19, 0.25]	.04
BMI x F CAP 3	.09	0.89	0.57	.115	[-0.22, 2.01]	.05
BMI x F CAP 4	-.04	-0.46	0.65	.481	[-0.15, 0.07]	.04
BMI x F CAP 5	-.03	-0.36	0.62	.559	[-0.14, 0.08]	.04
BMI X Transitions	.07	0.003	0.002	.219	[-0.002, 0.01]	.04

Fluency

BMI x DT CAP 1	.08	0.04	0.04	.217	[-0.03, 0.11]	.01
BMI x DT CAP 2	-.04	-0.02	0.03	.524	[-0.07, 0.04]	.01
BMI x DT CAP 3	-.01	-0.004	0.03	.903	[-0.06, 0.06]	.01
BMI x DT CAP 4	.12	0.05	0.03	.083	[-0.01, 0.25]	.02

BMI x DT CAP 5	-.07	-0.03	0.03	.309	[-0.07, 0.02]	.01
BMI x F CAP 1	-.02	-0.21	0.58	.711	[-1.35, 0.92]	.01
BMI x F CAP 2	-.06	-0.48	0.53	.366	[-1.51, 0.56]	.02
BMI x F CAP 3	.40	0.40	0.51	.433	[-0.60, 1.40]	.02
BMI x F CAP 4	.11	0.96	0.60	.110	[-0.22, 2.13]	.02
BMI x F CAP 5	-.08	-0.65	0.56	.243	[-1.75, 0.44]	.01
BMI X Transitions	-.02	-0.001	0.002	.730	[-0.01, 0.003]	.01

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

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

Figure 5

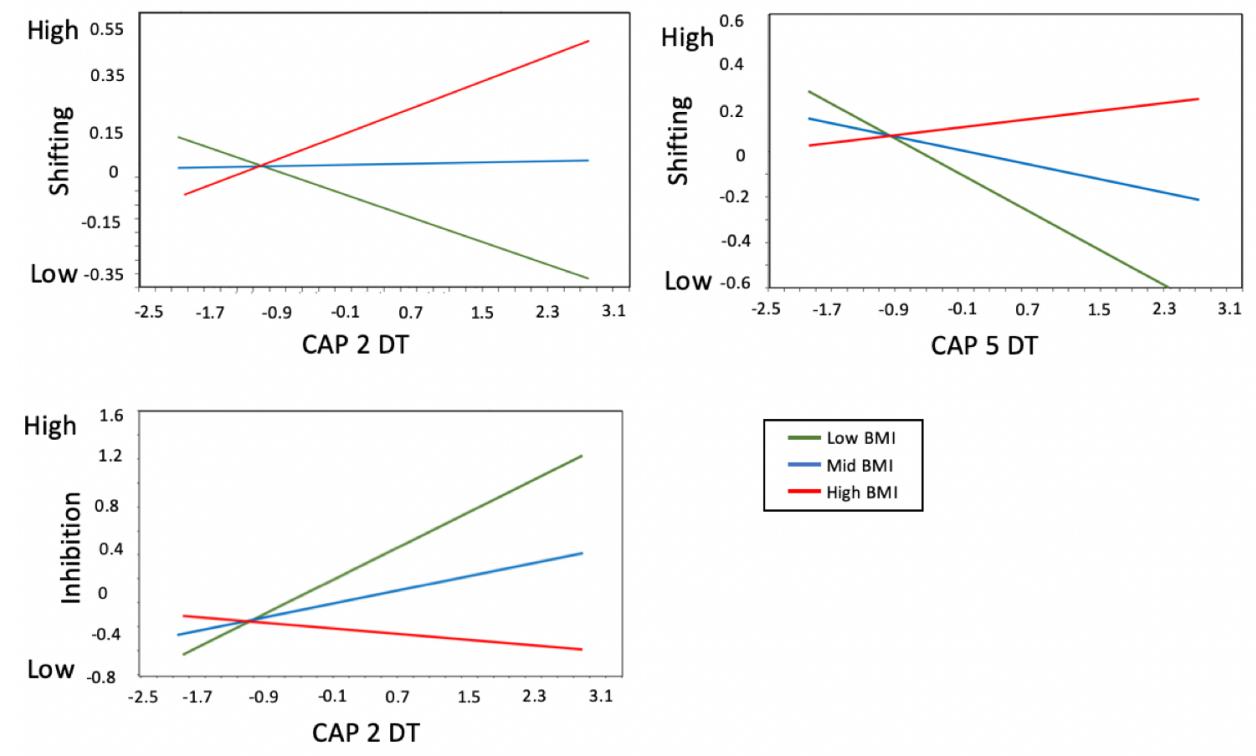


Figure 5. Simple Slopes

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

Main Effects

Non-significant 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, $b = -0.83$, $SE = 0.41$, $p = .044$, 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 executive function (EF).

The current 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 structural equation model (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 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 resting-state fMRI 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 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 bi-directional 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 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 the relationship between brain dynamics and EF is moderated by BMI during young to middle-aged adulthood.

The literature also suggests 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 the present 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 greater neural flexibility is associated with greater cognitive performance (71,118–120). In a study that examined brain dynamics in 19-80 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 was observed in individuals with a higher BMI compared to individuals with average and lower BMIs, indicating in overweight/obese individuals, a shorter dwell time 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 the current study, the relationship between brain dynamics and shifting depended 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 non-significant interactions, 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 the current 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 the current 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 remains 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 pro-inflammatory 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 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 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 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, 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 the present 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 the current study’s sample, a mediation analysis was not tested (151–155). Growing evidence in children and older adult populations suggest 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 the current 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, L-FPN and lower processing 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 brain network dynamics underlying EF depend on BMI, and that in future studies, BMI should be considered when studying brain network dynamics.

References

1. . Delis DC, Kaplan E, . Kramer JH. Delis-Kaplan Executive Function System: D-KEFS. 2001. 144 p.
2. 2015 GB of DS. Global Burden of Disease Study 2015 (GBD 2015) Obesity and Overweight Prevalence 1980--2015. United States: Institute for Health Metrics and Evaluation (IHME) Seattle; 2017.
3. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity and severe obesity among adults: United States, 2017--2018. 2020; Available from: <https://stacks.cdc.gov/view/cdc/85451>
4. Organization WH, Others. Obesity and overweight. Geneva. World Health Organization. 2017;
5. Huang Y, Lu Y, Huang Y-M, Wang M, Ling W, Sui Y, et al. Obesity in patients with COVID-19: a systematic review and meta-analysis. Metabolism. 2020 Sep 28;113:154378.
6. Singh GM, Danaei G, Farzadfar F, Stevens GA, Woodward M, Wormser D, et al. The age-specific quantitative effects of metabolic risk factors on cardiovascular diseases and diabetes: a pooled analysis. PLoS One. 2013 Jul 30;8(7):e65174.
7. Miller AA, Spencer SJ. Obesity and neuroinflammation: a pathway to cognitive impairment. Brain Behav Immun. 2014 Nov;42:10–21.
8. Rochette AD, Spitznagel MB, Strain G, Devlin M, Crosby RD, Mitchell JE, et al. Mild cognitive impairment is prevalent in persons with severe obesity. Obesity . 2016 Jul;24(7):1427–9.
9. Fitzpatrick AL, Kuller LH, Lopez OL, Diehr P, O'Meara ES, Longstreth WT Jr, et al. Midlife and late-life obesity and the risk of dementia: cardiovascular health study. Arch Neurol. 2009 Mar;66(3):336–42.

10. Bocarsly ME, Fasolino M, Kane GA, LaMarca EA, Kirschen GW, Karatsoreos IN, et al. Obesity diminishes synaptic markers, alters microglial morphology, and impairs cognitive function. *Proc Natl Acad Sci U S A.* 2015 Dec 22;112(51):15731–6.
11. Smith E, Hay P, Campbell L, Trollor JN. A review of the association between obesity and cognitive function across the lifespan: implications for novel approaches to prevention and treatment. *Obes Rev.* 2011 Sep;12(9):740–55.
12. Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry CP Jr, Yaffe K. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. *BMJ.* 2005 Jun 11;330(7504):1360.
13. Gunstad J, Paul RH, Cohen RA, Tate DF, Spitznagel MB, Grieve S, et al. Relationship between body mass index and brain volume in healthy adults. *Int J Neurosci.* 2008 Nov;118(11):1582–93.
14. Fitzpatrick S, Gilbert S, Serpell L. Systematic review: are overweight and obese individuals impaired on behavioural tasks of executive functioning? *Neuropsychol Rev.* 2013 Jun;23(2):138–56.
15. Yang Y, Shields GS, Guo C, Liu Y. Executive function performance in obesity and overweight individuals: A meta-analysis and review. *Neurosci Biobehav Rev.* 2018 Jan;84:225–44.
16. Diamond A. Executive functions. *Annu Rev Psychol.* 2013;64:135–68.
17. Doebel S. Rethinking Executive Function and Its Development. *Perspect Psychol Sci.* 2020 Jul;15(4):942–56.
18. Bailey CE. Cognitive accuracy and intelligent executive function in the brain and in business. *Ann N Y Acad Sci.* 2007 Nov;1118:122–41.
19. Madjar N, Chubarov E, Zalsman G, Weiser M, Shoval G. Social skills, executive functioning and social engagement. *Schizophr Res Cogn.* 2019 Sep;17:100137.
20. Leung RC, Vogan VM, Powell TL, Anagnostou E, Taylor MJ. The role of executive functions in social impairment in Autism Spectrum Disorder. *Child Neuropsychol.* 2016;22(3):336–44.
21. Brown TE, Landgraf JM. 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 [Internet]. Vol. 122, Postgraduate Medicine. 2010. p. 42–51. Available from: <http://dx.doi.org/10.3810/pgm.2010.09.2200>
22. Miyake A, Friedman NP. The Nature and Organization of Individual Differences in Executive Functions: Four General Conclusions. *Curr Dir Psychol Sci.* 2012

Feb;21(1):8–14.

23. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The Unity and Diversity of Executive Functions and Their Contributions to Complex “Frontal Lobe” Tasks: A Latent Variable Analysis. *Cogn Psychol*. 2000 Aug 1;41(1):49–100.
24. Testa R, Bennett P, Ponsford J. Factor analysis of nineteen executive function tests in a healthy adult population. *Arch Clin Neuropsychol*. 2012 Mar;27(2):213–24.
25. Morris L, Mansell W. A systematic review of the relationship between rigidity/flexibility and transdiagnostic cognitive and behavioral processes that maintain psychopathology. *J Exp Psychopathol*. 2018 Jul 1;9(3):2043808718779431.
26. Tavares JVT, Taylor Tavares JV, Clark L, Cannon DM, Erickson K, Drevets WC, et al. Distinct Profiles of Neurocognitive Function in Unmedicated Unipolar Depression and Bipolar II Depression [Internet]. Vol. 62, *Biological Psychiatry*. 2007. p. 917–24. Available from: <http://dx.doi.org/10.1016/j.biopsych.2007.05.034>
27. van Vuuren CL, Wachter GG, Veenstra R, Rijnhart JJM, van der Wal MF, Chinapaw MJM, et al. Associations between overweight and mental health problems among adolescents, and the mediating role of victimization. *BMC Public Health*. 2019 May 21;19(1):612.
28. Simon GE, Von Korff M, Saunders K, Miglioretti DL, Crane PK, van Belle G, et al. Association between obesity and psychiatric disorders in the US adult population. *Arch Gen Psychiatry*. 2006 Jul;63(7):824–30.
29. Floyd RG, Bergeron R, Hamilton G, Parra GR. 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 [Internet]. *Psychology in the Schools*. 2010. Available from: <http://dx.doi.org/10.1002/pits.20500>
30. Latzman RD, Markon KE. The factor structure and age-related factorial invariance of the Delis-Kaplan Executive Function System (D-KEFS). *Assessment*. 2010 Jun;17(2):172–84.
31. Bollen KA. Structural Equations with Latent Variables [Internet]. 1989. Available from: <http://dx.doi.org/10.1002/9781118619179>
32. Friedman NP, Miyake A, Young SE, DeFries JC, Corley RP, Hewitt JK. Individual differences in executive functions are almost entirely genetic in origin. *J Exp Psychol Gen*. 2008 May;137(2):201–25.
33. Karr JE, Hofer SM, Iverson GL, Garcia-Barrera MA. Examining the latent structure of the Delis-Kaplan executive function system. *Arch Clin Neuropsychol*. 2019;34(3):381–94.
34. Dajani DR, Uddin LQ. Demystifying cognitive flexibility: Implications for clinical and

- developmental neuroscience. *Trends Neurosci.* 2015 Sep;38(9):571–8.
35. Shao Z, Janse E, Visser K, Meyer AS. What do verbal fluency tasks measure? Predictors of verbal fluency performance in older adults. *Front Psychol.* 2014 Jul 22;5:772.
 36. Suchy Y, Kraybill ML, Gidley Larson JC. Understanding design fluency: motor and executive contributions. *J Int Neuropsychol Soc.* 2010 Jan;16(1):26–37.
 37. Donofry SD, Stillman CM, Erickson KI. A review of the relationship between eating behavior, obesity and functional brain network organization. *Soc Cogn Affect Neurosci.* 2020 Nov 10;15(10):1157–81.
 38. Wijngaarden MA, Veer IM, Rombouts SARB, van Buchem MA, Willems van Dijk K, Pijl H, et al. Obesity is marked by distinct functional connectivity in brain networks involved in food reward and salience. *Behav Brain Res.* 2015 Mar 14;287:127–34.
 39. Geha P, Cecchi G, Todd Constable R, Abdallah C, Small DM. Reorganization of brain connectivity in obesity. *Hum Brain Mapp.* 2017 Mar;38(3):1403–20.
 40. Nummenmaa L, Hirvonen J, Hannukainen JC, Immonen H, Lindroos MM, Salminen P, et al. Dorsal striatum and its limbic connectivity mediate abnormal anticipatory reward processing in obesity. *PLoS One.* 2012 Feb 3;7(2):e31089.
 41. Kullmann S, Pape A-A, Heni M, Ketterer C, Schick F, Häring H-U, et al. Functional network connectivity underlying food processing: disturbed salience and visual processing in overweight and obese adults. *Cereb Cortex.* 2013 May;23(5):1247–56.
 42. Kube J, Mathar D, Horstmann A, Kotz SA, Villringer A, Neumann J. Altered monetary loss processing and reinforcement-based learning in individuals with obesity. *Brain Imaging Behav.* 2018 Oct;12(5):1431–49.
 43. Atalayer D, Pantazatos SP, Gibson CD, McOuatt H, Puma L, Astbury NM, et al. Sexually dimorphic functional connectivity in response to high vs. low energy-dense food cues in obese humans: an fMRI study. *Neuroimage.* 2014 Oct 15;100:405–13.
 44. Lips MA, Wijngaarden MA, van der Grond J, van Buchem MA, de Groot GH, Rombouts SARB, et al. Resting-state functional connectivity of brain regions involved in cognitive control, motivation, and reward is enhanced in obese females. *Am J Clin Nutr.* 2014 Aug;100(2):524–31.
 45. Sadler JR, Shearrer GE, Burger KS. Body mass variability is represented by distinct functional connectivity patterns. *Neuroimage.* 2018 Nov 1;181:55–63.
 46. Uddin LQ, Yeo BTT, Spreng RN. Towards a Universal Taxonomy of Macro-scale Functional Human Brain Networks. *Brain Topogr.* 2019 Nov;32(6):926–42.
 47. Uddin LQ, Supekar K, Lynch CJ, Cheng KM, Odriozola P, Barth ME, et al. Brain State

Differentiation and Behavioral Inflexibility in Autism. *Cereb Cortex*. 2015 Dec;25(12):4740–7.

48. Syan SK, Owens MM, Goodman B, Epstein LH, Meyre D, Sweet LH, et al. Deficits in executive function and suppression of default mode network in obesity. *Neuroimage Clin*. 2019 Oct 26;24:102015.
49. Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. *Trends Cogn Sci*. 2011 Oct;15(10):483–506.
50. García-García I, Jurado MA, Garolera M, Segura B, Marqués-Iturria I, Pueyo R, et al. Functional connectivity in obesity during reward processing [Internet]. Vol. 66, *NeuroImage*. 2013. p. 232–9. Available from: <http://dx.doi.org/10.1016/j.neuroimage.2012.10.035>
51. Doucet GE, Rasgon N, McEwen BS, Micali N, Frangou S. Elevated Body Mass Index is Associated with Increased Integration and Reduced Cohesion of Sensory-Driven and Internally Guided Resting-State Functional Brain Networks [Internet]. Vol. 28, *Cerebral Cortex*. 2018. p. 988–97. Available from: <http://dx.doi.org/10.1093/cercor/bhx008>
52. Cohen JI, Yates KF, Duong M, Convit A. Obesity, orbitofrontal structure and function are associated with food choice: a cross-sectional study [Internet]. Vol. 1, *BMJ Open*. 2011. p. e000175–e000175. Available from: <http://dx.doi.org/10.1136/bmjopen-2011-000175>
53. Kishinevsky FI, Cox JE, Murdaugh DL, Stoeckel LE, Cook EW 3rd, Weller RE. fMRI reactivity on a delay discounting task predicts weight gain in obese women. *Appetite*. 2012 Apr;58(2):582–92.
54. Maayan L, Hoogendoorn C, Sweat V, Convit A. Disinhibited eating in obese adolescents is associated with orbitofrontal volume reductions and executive dysfunction. *Obesity*. 2011 Jul;19(7):1382–7.
55. Nomi JS, Vij SG, Dajani DR, Steimke R, Damaraju E, Rachakonda S, et al. Chronnectomic patterns and neural flexibility underlie executive function. *Neuroimage*. 2017 Feb 15;147:861–71.
56. Park B-Y, Moon T, Park H. Dynamic functional connectivity analysis reveals improved association between brain networks and eating behaviors compared to static analysis. *Behav Brain Res*. 2018 Jan 30;337:114–21.
57. Knight SP, Laird E, Williamson W, O'Connor J, Newman L, Carey D, et al. Obesity is associated with reduced cerebral blood flow – modified by physical activity. *Neurobiol Aging*. 2021 Sep 1;105:35–47.
58. Simon AB, Buxton RB. Understanding the dynamic relationship between cerebral blood flow and the BOLD signal: Implications for quantitative functional MRI. *Neuroimage*. 2015

- Aug 1;116:158–67.
59. Iadecola C. Neurovascular regulation in the normal brain and in Alzheimer's disease. *Nat Rev Neurosci*. 2004 May;5(5):347–60.
 60. Attwell D, Laughlin SB. An energy budget for signaling in the grey matter of the brain. *J Cereb Blood Flow Metab*. 2001 Oct;21(10):1133–45.
 61. Tak S, Polimeni JR, Wang DJJ, Yan L, Chen JJ. Associations of resting-state fMRI functional connectivity with flow-BOLD coupling and regional vasculature. *Brain Connect*. 2015 Apr;5(3):137–46.
 62. Lurie DJ, Kessler D, Bassett DS, Betzel RF, Breakspear M, Kheilholz S, et al. Questions and controversies in the study of time-varying functional connectivity in resting fMRI. *Netw Neurosci*. 2020 Feb 1;4(1):30–69.
 63. Lewis N, Lu H, Liu P, Hou X, Damaraju E, Iraji A, et al. Static and dynamic functional connectivity analysis of cerebrovascular reactivity: An fMRI study. *Brain Behav*. 2020 Jun;10(6):e01516.
 64. Kupis L, Goodman ZT, Kircher L, Romero C, Dirks B, Chang C, et al. Altered patterns of brain dynamics linked with body mass index in youth with autism. *Autism Res [Internet]*. 2021 Feb 22; Available from: <http://dx.doi.org/10.1002/aur.2488>
 65. Gertel VH, Zhang H, Diaz MT. Stronger right hemisphere functional connectivity supports executive aspects of language in older adults. *Brain Lang*. 2020 Jul;206:104771.
 66. Nguyen-Rodriguez ST, Chou C-P, Unger JB, Spruijt-Metz D. BMI as a moderator of perceived stress and emotional eating in adolescents. *Eat Behav*. 2008 Apr;9(2):238–46.
 67. Abshire DA, Lennie TA, Chung ML, Biddle MJ, Barbosa-Leiker C, Moser DK. Body Mass Index Category Moderates the Relationship Between Depressive Symptoms and Diet Quality in Overweight and Obese Rural-Dwelling Adults. *J Rural Health*. 2018 Sep;34(4):377–87.
 68. Baron RM, Kenny DA. The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *J Pers Soc Psychol*. 1986 Dec;51(6):1173–82.
 69. Hartanto A, Yong JC, Toh WX. Bidirectional Associations between Obesity and Cognitive Function in Midlife Adults: A Longitudinal Study. *Nutrients [Internet]*. 2019 Oct 2;11(10). Available from: <http://dx.doi.org/10.3390/nu11102343>
 70. Cunningham GB, Ahn NY. Moderation in sport management research: room for growth. *Meas Phys Educ Exerc Sci*. 2019 Oct 2;23(4):301–13.
 71. Hutchison RM, Morton JB. Tracking the Brain's Functional Coupling Dynamics over

- Development. *J Neurosci*. 2015 Apr 29;35(17):6849–59.
- 72. Park DC, Lautenschlager G, Hedden T, Davidson NS, Smith AD, Smith PK. Models of visuospatial and verbal memory across the adult life span. *Psychol Aging*. 2002 Jun;17(2):299–320.
 - 73. Li Y, Gao J, Enkavi AZ, Zaval L, Weber EU, Johnson EJ. Sound credit scores and financial decisions despite cognitive aging. *Proc Natl Acad Sci U S A*. 2015 Jan 6;112(1):65–9.
 - 74. Samanez-Larkin GR, Knutson B. Decision making in the ageing brain: changes in affective and motivational circuits. *Nat Rev Neurosci*. 2015 May;16(5):278–89.
 - 75. Narimani M, Esmaeilzadeh S, Azevedo LB, Moradi A, Heidari B, Kashfi-Moghadam M. Association Between Weight Status and Executive Function in Young Adults. *Medicina [Internet]*. 2019 Jul 10;55(7). Available from: <http://dx.doi.org/10.3390/medicina55070363>
 - 76. Prickett C, Brennan L, Stolwyk R. Examining the relationship between obesity and cognitive function: a systematic literature review. *Obes Res Clin Pract*. 2015 Mar;9(2):93–113.
 - 77. Chang C, Glover GH. Time–frequency dynamics of resting-state brain connectivity measured with fMRI. *Neuroimage*. 2010 Mar 1;50(1):81–98.
 - 78. Sakoğlu U, Pearson GD, Kiehl KA, Wang YM, Michael AM, Calhoun VD. A method for evaluating dynamic functional network connectivity and task-modulation: application to schizophrenia. *MAGMA*. 2010 Dec;23(5-6):351–66.
 - 79. Liu X, Duyn JH. Time-varying functional network information extracted from brief instances of spontaneous brain activity. *Proc Natl Acad Sci U S A*. 2013 Mar 12;110(11):4392–7.
 - 80. Jin C, Jia H, Lanka P, Rangaprakash D, Li L, Liu T, et al. Dynamic brain connectivity is a better predictor of PTSD than static connectivity. *Hum Brain Mapp*. 2017 Sep;38(9):4479–96.
 - 81. Liégeois R, Li J, Kong R, Orban C, Van De Ville D, Ge T, et al. Resting brain dynamics at different timescales capture distinct aspects of human behavior. *Nat Commun*. 2019 May 24;10(1):2317.
 - 82. Liu X, Zhang N, Chang C, Duyn JH. Co-activation patterns in resting-state fMRI signals. *Neuroimage*. 2018 Oct 15;180(Pt B):485–94.
 - 83. Marshall E, Nomi JS, Dirks B, Romero C, Kupis L, Chang C, et al. Co-activation pattern analysis reveals altered salience network dynamics in children with autism spectrum disorder. *Network Neuroscience*. 2020 Aug 10;1–16.
 - 84. Kupis L, Romero C, Dirks B, Hoang S, Parlade MV, Beaumont AL, et al. Evoked and

- intrinsic brain network dynamics in children with autism spectrum disorder. *Neuroimage: Clinical*. 2020;
85. Qiao L, Xu M, Luo X, Zhang L, Li H, Chen A. Flexible adjustment of the effective connectivity between the fronto-parietal and visual regions supports cognitive flexibility. *Neuroimage*. 2020 Jul 11;220:117158.
 86. Homack S, Lee D, Riccio CA. Test review: Delis-Kaplan executive function system. *J Clin Exp Neuropsychol*. 2005 Jul;27(5):599–609.
 87. Yochim B, Baldo J, Nelson A, Delis DC. D-KEFS Trail Making Test performance in patients with lateral prefrontal cortex lesions. *J Int Neuropsychol Soc*. 2007 Jul;13(4):704–9.
 88. Yan C-G, Wang X-D, Zuo X-N, Zang Y-F. DPABI: Data Processing & Analysis for (Resting-State) Brain Imaging. *Neuroinformatics*. 2016 Jul;14(3):339–51.
 89. Griffanti L, Salimi-Khorshidi G, Beckmann CF, Auerbach EJ, Douaud G, Sexton CE, et al. ICA-based artefact removal and accelerated fMRI acquisition for improved resting state network imaging. *Neuroimage*. 2014 Jul 15;95:232–47.
 90. Schaefer A, Kong R, Gordon EM, Laumann TO, Zuo X-N, Holmes AJ, et al. Local-Global Parcellation of the Human Cerebral Cortex from Intrinsic Functional Connectivity MRI. *Cereb Cortex*. 2018 Sep 1;28(9):3095–114.
 91. Muthén BO, Muthén LK. IRT in Mplus. URL: <http://www.statmodel.com/irtanalysis.shtml> (visited on 12/08/2014). 2010;
 92. Muthén LK, Muthén B. Mplus Version 8 User’s Guide. Muthén & Muthén; 2017. 944 p.
 93. Guàrdia-Olmos J, Peró-Cebollero M, Gudayol-Ferré E. Meta-Analysis of the Structural Equation Models’ Parameters for the Estimation of Brain Connectivity with fMRI. *Front Behav Neurosci*. 2018 Feb 15;12:19.
 94. Beaty RE, Chen Q, Christensen AP, Qiu J, Silvia PJ, Schacter DL. Brain networks of the imaginative mind: Dynamic functional connectivity of default and cognitive control networks relates to openness to experience. *Hum Brain Mapp*. 2018 Feb;39(2):811–21.
 95. Frazier PA, Tix AP, Barron KE. Testing Moderator and Mediator Effects in Counseling Psychology Research [Internet]. Vol. 51, *Journal of Counseling Psychology*. 2004. p. 115–34. Available from: <http://dx.doi.org/10.1037/0022-0167.51.1.115>
 96. Iacobucci D, Schneider MJ, Popovich DL, Bakamitsos GA. Mean centering helps alleviate “micro” but not “macro” multicollinearity. *Behav Res Methods*. 2016 Dec 1;48(4):1308–17.
 97. Kelava A, Werner CS, Schermelleh-Engel K, Moosbrugger H, Zapf D, Ma Y, et al. Advanced Nonlinear Latent Variable Modeling: Distribution Analytic LMS and QML

- Estimators of Interaction and Quadratic Effects [Internet]. Vol. 18, Structural Equation Modeling: A Multidisciplinary Journal. 2011. p. 465–91. Available from: <http://dx.doi.org/10.1080/10705511.2011.582408>
98. Marsh HW, Hau K-T, Wen Z, Nagengast B, Morin AJS. Moderation. In: Little TD, editor. The Oxford handbook of quantitative methods: Statistical analysis, Vol. New York, NY, US: Oxford University Press, xviii; 2013. p. 361–86.
 99. Fairchild AJ, MacKinnon DP. A general model for testing mediation and moderation effects. *Prev Sci*. 2009 Jun;10(2):87–99.
 100. Cole DA, Nick EA, Varga G, Smith D, Zelkowitz RL, Ford MA, et al. Are Aspects of Twitter Use Associated with Reduced Depressive Symptoms? The Moderating Role of In-Person Social Support. *Cyberpsychol Behav Soc Netw*. 2019 Nov;22(11):692–9.
 101. Yap MBH, Whittle S, Yücel M, Sheeber L, Pantelis C, Simmons JG, et al. Interaction of parenting experiences and brain structure in the prediction of depressive symptoms in adolescents. *Arch Gen Psychiatry*. 2008 Dec;65(12):1377–85.
 102. Kim J, Zhu W, Chang L, Bentler PM, Ernst T. Unified structural equation modeling approach for the analysis of multisubject, multivariate functional MRI data. *Hum Brain Mapp*. 2007 Feb;28(2):85–93.
 103. Beets MW, Foley JT. Association of father involvement and neighborhood quality with kindergartners' physical activity: a multilevel structural equation model. *Am J Health Promot*. 2008 Jan;22(3):195–203.
 104. Asparouhov T, Muthén B. Exploratory Structural Equation Modeling. *Struct Equ Modeling*. 2009 Jul 14;16(3):397–438.
 105. Miller JW, Stromeyer WR, Schwieterman MA. Extensions of the Johnson-Neyman Technique to Linear Models With Curvilinear Effects: Derivations and Analytical Tools. *Multivariate Behav Res*. 2013 Mar;48(2):267–300.
 106. Karr JE, Hofer SM, Iverson GL. Examining the latent structure of the Delis–Kaplan executive function system. *Arch Clin Neuropsychol* [Internet]. 2019; Available from: <https://academic.oup.com/acn/article-abstract/34/3/381/4992688>
 107. Shefer G, Marcus Y, Stern N. Is obesity a brain disease? *Neurosci Biobehav Rev*. 2013 Dec;37(10 Pt 2):2489–503.
 108. García-García I, Jurado MÁ, Garolera M, Segura B, Sala-Llonch R, Marqués-Iturria I, et al. Alterations of the salience network in obesity: a resting-state fMRI study. *Hum Brain Mapp*. 2013;34(11):2786–97.
 109. Chao S-H, Liao Y-T, Chen VC-H, Li C-J, McIntyre RS, Lee Y, et al. Correlation between

- brain circuit segregation and obesity. *Behav Brain Res.* 2018 Jan 30;337:218–27.
110. Alosco ML, Galioto R, Spitznagel MB, Others. Cognitive function following bariatric surgery: Evidence for improvement 3 years post-surgery. *Am J Surg.* 2013;
111. Prehn K, Jumperz von Schwartzenberg R, Mai K, Zeitz U, Witte AV, Hampel D, et al. Caloric restriction in older adults—differential effects of weight loss and reduced weight on brain structure and function. *Cereb Cortex.* 2017;27(3):1765–78.
112. Frank S, Wilms B, Veit R, Ernst B, Thurnheer M, Kullmann S, et al. Altered brain activity in severely obese women may recover after Roux-en Y gastric bypass surgery. *Int J Obes.* 2014 Mar;38(3):341–8.
113. Coveleskie K, Gupta A, Kilpatrick LA, Mayer ED, Ashe-McNalley C, Stains J, et al. Altered functional connectivity within the central reward network in overweight and obese women. *Nutr Diabetes.* 2015 Jan 19;5:e148.
114. Park B-Y, Byeon K, Lee MJ, Chung C-S, Kim S-H, Morys F, et al. Whole-brain functional connectivity correlates of obesity phenotypes. *Hum Brain Mapp [Internet].* 2020; Available 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. Obesity is associated with altered mid-insula functional connectivity to limbic regions underlying appetitive responses to foods. *J Psychopharmacol.* 2017 Nov;31(11):1475–84.
116. Contreras-Rodríguez O, Martín-Pérez C, Vilar-López R, Verdejo-Garcia A. Ventral and Dorsal Striatum Networks in Obesity: Link to Food Craving and Weight Gain. *Biol Psychiatry.* 2017 May 1;81(9):789–96.
117. Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci.* 2002 Mar;3(3):201–15.
118. Grady CL, Garrett DD. Understanding variability in the BOLD signal and why it matters for aging. *Brain Imaging Behav.* 2014 Jun;8(2):274–83.
119. Kumral D, Şansal F, Cesnaite E, Mahjoory K, Al E, Gaebler M, et al. BOLD and EEG signal variability at rest differently relate to aging in the human brain. *Neuroimage.* 2020 Feb 15;207:116373.
120. Xia Y, Chen Q, Shi L, Li M, Gong W, Chen H, et al. Tracking the dynamic functional connectivity structure of the human brain across the adult lifespan. *Hum Brain Mapp.* 2019 Feb 15;40(3):717–28.
121. Shine JM, Bissett PG, Bell PT, Koyejo O, Balsters JH, Gorgolewski KJ, et al. The Dynamics of Functional Brain Networks: Integrated Network States during Cognitive Task Performance. *Neuron.* 2016 Oct 19;92(2):544–54.

122. Baek K, Morris LS, Kundu P, Voon V. Disrupted resting-state brain network properties in obesity: decreased global and putaminal cortico-striatal network efficiency. *Psychol Med.* 2017 Mar;47(4):585–96.
123. Stanley ML, Simpson SL, Dagenbach D, Lyday RG, Burdette JH, Laurienti PJ. Changes in brain network efficiency and working memory performance in aging. *PLoS One.* 2015 Apr 13;10(4):e0123950.
124. Lawrence AJ, Chung AW, Morris RG, Markus HS, Barrick TR. Structural network efficiency is associated with cognitive impairment in small-vessel disease. *Neurology.* 2014 Jul 22;83(4):304–11.
125. Chén OY, Cao H, Reinen JM, Qian T, Gou J, Phan H, et al. Resting-state brain information flow predicts cognitive flexibility in humans. *Sci Rep.* 2019 Mar 7;9(1):3879.
126. Bagarinao E, Watanabe H, Maesawa S, Mori D, Hara K, Kawabata K, et al. Reorganization of brain networks and its association with general cognitive performance over the adult lifespan. *Sci Rep.* 2019 Aug 6;9(1):11352.
127. Hoff GEA-J, Van den Heuvel MP, Benders MJNL, Kersbergen KJ, De Vries LS. On development of functional brain connectivity in the young brain. *Front Hum Neurosci.* 2013 Oct 8;7:650.
128. Xu X, Hanganu-Opatz IL, Bieler M. Cross-Talk of Low-Level Sensory and High-Level Cognitive Processing: Development, Mechanisms, and Relevance for Cross-Modal Abilities of the Brain. *Front Neurorobot.* 2020 Feb 14;14:7.
129. Denervaud S, Gentaz E, Matusz PJ, Murray MM. Multisensory Gains in Simple Detection Predict Global Cognition in Schoolchildren. *Sci Rep.* 2020 Feb 4;10(1):1394.
130. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med.* 1996 Feb 1;334(5):292–5.
131. Enriori PJ, Evans AE, Sinnayah P, Cowley MA. Leptin resistance and obesity. *Obesity.* 2006 Aug;14 Suppl 5:254S – 258S.
132. Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. *Annu Rev Immunol.* 2011;29:415–45.
133. Nguyen JCD, Killcross AS, Jenkins TA. Obesity and cognitive decline: role of inflammation and vascular changes. *Front Neurosci.* 2014 Nov 19;8:375.
134. Tan ZS, Beiser AS, Fox CS, Au R, Himali JJ, Debette S, et al. 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. 2011 Aug;34(8):1766–70.
135. Trollor JN, Smith E, Baune BT, Kochan NA, Campbell L, Samaras K, et al. Systemic inflammation is associated with MCI and its subtypes: the Sydney Memory and Aging Study. *Dement Geriatr Cogn Disord*. 2010;30(6):569–78.
 136. Baune BT, Ponath G, Golledge J, Varga G, Arolt V, Rothermundt M, et al. Association between IL-8 cytokine and cognitive performance in an elderly general population—The MEMO-Study. *Neurobiol Aging*. 2008 Jun 1;29(6):937–44.
 137. Raz N, Rodriguez KM. Differential aging of the brain: patterns, cognitive correlates and modifiers. *Neurosci Biobehav Rev*. 2006 Aug 17;30(6):730–48.
 138. Hull JV, Dokovna LB, Jacokes ZJ, Torgerson CM, Irimia A, Van Horn JD, et al. Corrigendum: Resting-State Functional Connectivity in Autism Spectrum Disorders: A Review. *Front Psychiatry*. 2018 Jun 22;9:268.
 139. Bos DJ, van Raalten TR, Oranje B, Smits AR, Kobussen NA, van Belle J, et al. Developmental differences in higher-order resting-state networks in Autism Spectrum Disorder. *Neuroimage Clin*. 2014 May 14;4:820–7.
 140. Cerliani L, Mennes M, Thomas RM, Di Martino A, Thioux M, Keysers C. Increased Functional Connectivity Between Subcortical and Cortical Resting-State Networks in Autism Spectrum Disorder. *JAMA Psychiatry*. 2015 Aug;72(8):767–77.
 141. Ebisch SJH, Gallese V, Willems RM, Mantini D, Groen WB, Romani GL, et al. Altered intrinsic functional connectivity of anterior and posterior insula regions in high-functioning participants with autism spectrum disorder. *Hum Brain Mapp*. 2011;32(7):1013–28.
 142. Keown CL, Shih P, Nair A, Peterson N, Mulvey ME, Müller R-A. Local functional overconnectivity in posterior brain regions is associated with symptom severity in autism spectrum disorders. *Cell Rep*. 2013 Nov 14;5(3):567–72.
 143. Jacob S, Wolff JJ, Steinbach MS, Doyle CB, Kumar V, Elison JT. Neurodevelopmental heterogeneity and computational approaches for understanding autism. *Transl Psychiatry*. 2019 Feb 4;9(1):63.
 144. Kahathuduwa CN, West BD, Blume J, Dharavath N, Moustaid-Moussa N, Mastergeorge A. The risk of overweight and obesity in children with autism spectrum disorders: A systematic review and meta-analysis. *Obes Rev*. 2019 Dec 8;20(12):1667–79.
 145. Sedgewick F, Leppanen J, Tchanturia K. Autistic adult outcomes on weight and body mass index: a large-scale online study. *Eat Weight Disord*. 2020 Jun;25(3):795–801.
 146. Pedhazur EJ. Multiple Regression in Behavioral Research: Explanation and Prediction. Harcourt Brace College Publishers; 1997. 1058 p.

147. Berg EA. A Simple Objective Technique for Measuring Flexibility in Thinking [Internet]. Vol. 39, The Journal of General Psychology. 1948. p. 15–22. Available from: <http://dx.doi.org/10.1080/00221309.1948.9918159>
148. Allen EA, Damaraju E, Plis SM, Erhardt EB, Eichele T, Calhoun VD. Tracking whole-brain connectivity dynamics in the resting state. *Cereb Cortex*. 2014 Mar;24(3):663–76.
149. Nilsson L-G, Nilsson E. Overweight and cognition. *Scand J Psychol*. 2009 Dec;50(6):660–7.
150. Childers DK, Allison DB. The “obesity paradox”: a parsimonious explanation for relations among obesity, mortality rate and aging? *Int J Obes*. 2010 Aug;34(8):1231–8.
151. Cole DA, Maxwell SE. Testing mediational models with longitudinal data: questions and tips in the use of structural equation modeling. *J Abnorm Psychol*. 2003 Nov;112(4):558–77.
152. Maxwell SE, Cole DA. Bias in cross-sectional analyses of longitudinal mediation. *Psychol Methods*. 2007 Mar;12(1):23–44.
153. Maxwell SE, Cole DA, Mitchell MA. Bias in Cross-Sectional Analyses of Longitudinal Mediation: Partial and Complete Mediation Under an Autoregressive Model [Internet]. Vol. 46, *Multivariate Behavioral Research*. 2011. p. 816–41. Available from: <http://dx.doi.org/10.1080/00273171.2011.606716>
154. American Psychopathological Association. Meeting. Causality and Psychopathology: Finding the Determinants of Disorders and Their Cures. Oxford University Press, USA; 2011. 364 p.
155. Shrout PE. Commentary: Mediation Analysis, Causal Process, and Cross-Sectional Data. *Multivariate Behav Res*. 2011 Sep 30;46(5):852–60.
156. Bischof GN, Park DC. Obesity and Aging: Consequences for Cognition, Brain Structure, and Brain Function. *Psychosom Med*. 2015 Jul;77(6):697–709.
157. Laurent JS, Watts R, Adise S, Allgaier N, Chaarani B, Garavan H, et al. Associations Among Body Mass Index, Cortical Thickness, and Executive Function in Children. *JAMA Pediatr*. 2020 Feb 1;174(2):170–7.
158. Shields GS, Moons WG, Slavich GM. Inflammation, Self-Regulation, and Health: An Immunologic Model of Self-Regulatory Failure. *Perspect Psychol Sci*. 2017 Jul;12(4):588–612.
159. Raemaekers M, Schellekens W, Petridou N, Ramsey NF. Knowing left from right: asymmetric functional connectivity during resting state. *Brain Struct Funct*. 2018

May;223(4):1909–22.

160. Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, et al. Correspondence of the brain's functional architecture during activation and rest. *Proc Natl Acad Sci U S A*. 2009 Aug 4;106(31):13040–5.
161. Nomi JS, Uddin LQ. Developmental changes in large-scale network connectivity in autism. *Neuroimage Clin*. 2015 Mar 6;7:732–41.
162. Agcaoglu O, Miller R, Mayer AR, Hugdahl K, Calhoun VD. Lateralization of resting state networks and relationship to age and gender. *Neuroimage*. 2015 Jan 1;104:310–25.
163. Murphy K, Fox MD. Towards a consensus regarding global signal regression for resting state functional connectivity MRI. *Neuroimage*. 2017 Jul 1;154:169–73.
164. Ceric R, Rosen AFG, Erus G, Cieslak M, Adebimpe A, Cook PA, et al. Mitigating head motion artifact in functional connectivity MRI. *Nat Protoc*. 2018 Dec;13(12):2801–26.
165. Power JD, Plitt M, Laumann TO, Martin A. Sources and implications of whole-brain fMRI signals in humans. *Neuroimage*. 2017 Feb 1;146:609–25.
166. Hyder F, Rothman DL. Neuronal correlate of BOLD signal fluctuations at rest: err on the side of the baseline. *Proc Natl Acad Sci U S A*. 2010 Jun 15;107(24):10773–4.
167. Schölvinck ML, Maier A, Ye FQ, Duyn JH, Leopold DA. Neural basis of global resting-state fMRI activity. *Proc Natl Acad Sci U S A*. 2010 Jun 1;107(22):10238–43.
168. Wang J, Wang X. Structural Equation Modeling: Applications Using Mplus. John Wiley & Sons; 2019. 536 p.
169. Sardeshmukh SR, Vandenberg RJ. Integrating Moderation and Mediation: A Structural Equation Modeling Approach. *Organizational Research Methods*. 2017 Oct 1;20(4):721–45.

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 5 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, 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 6 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) was still present while predicting shifting, $b = 0.06$, $SE = 0.03$, $p = .025$, 95% CI [0.01, 0.11], but not inhibition, $b = -0.06$, $SE =$

$0.04, p = .108$, 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, $b = 0.07, SE = 0.03, p = .007$, 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, $b = -0.88, SE = 0.42, p = .039$, 95% CI [-1.71, -0.04].

Bootstrapping

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

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) was still present while predicting shifting, $b = 0.05, SE = 0.03, p = .039$, 95% CI [0.004, 0.11], but not inhibition, $b = -0.07, SE = 0.03, p = .054$, 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, $b = 0.06, SE = 0.03, p = .023$, 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, $b = -0.90$, $SE = 0.43$, $p = .039$, 95% CI [-1.78, -0.05].

Figure S1

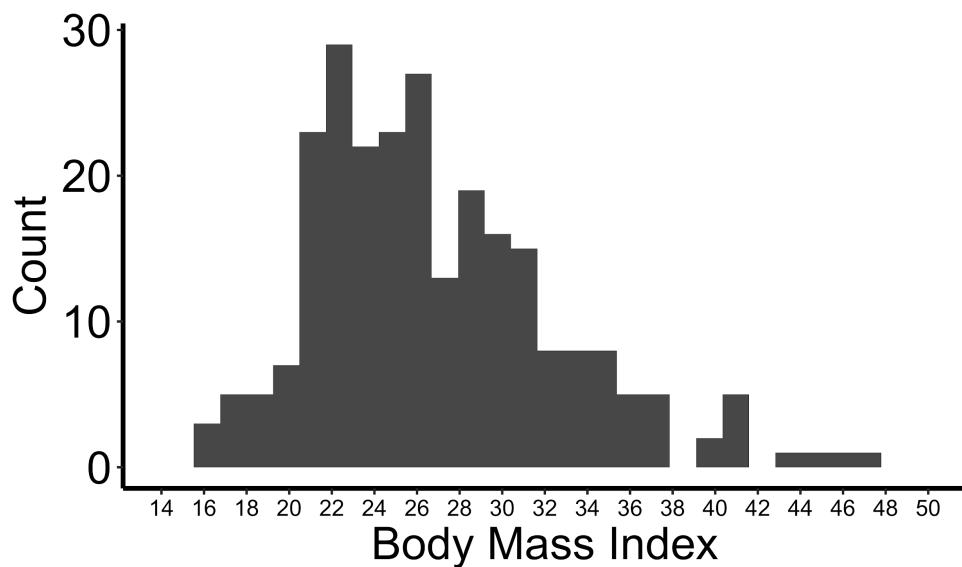


Figure S1. Distribution of Body Mass Index

Figure S2

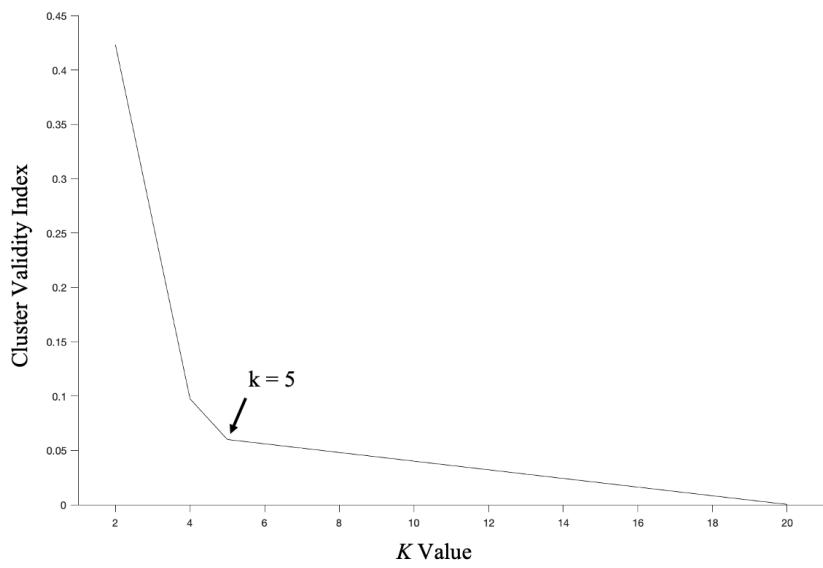


Figure S2. Elbow Criterion

The elbow criterion identifies $k = 5$ clusters.

Figure S3

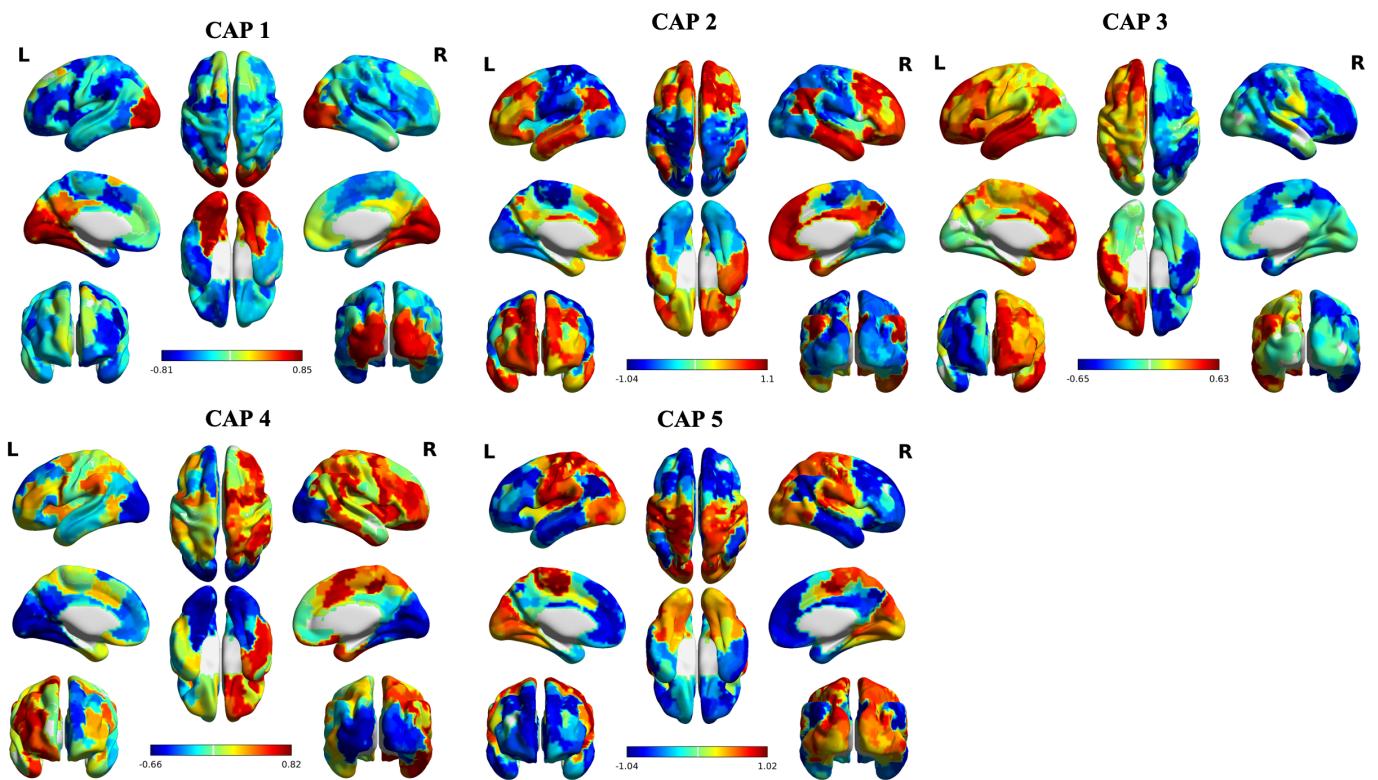


Figure S3. Co-activation Patterns

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.

Figure S4

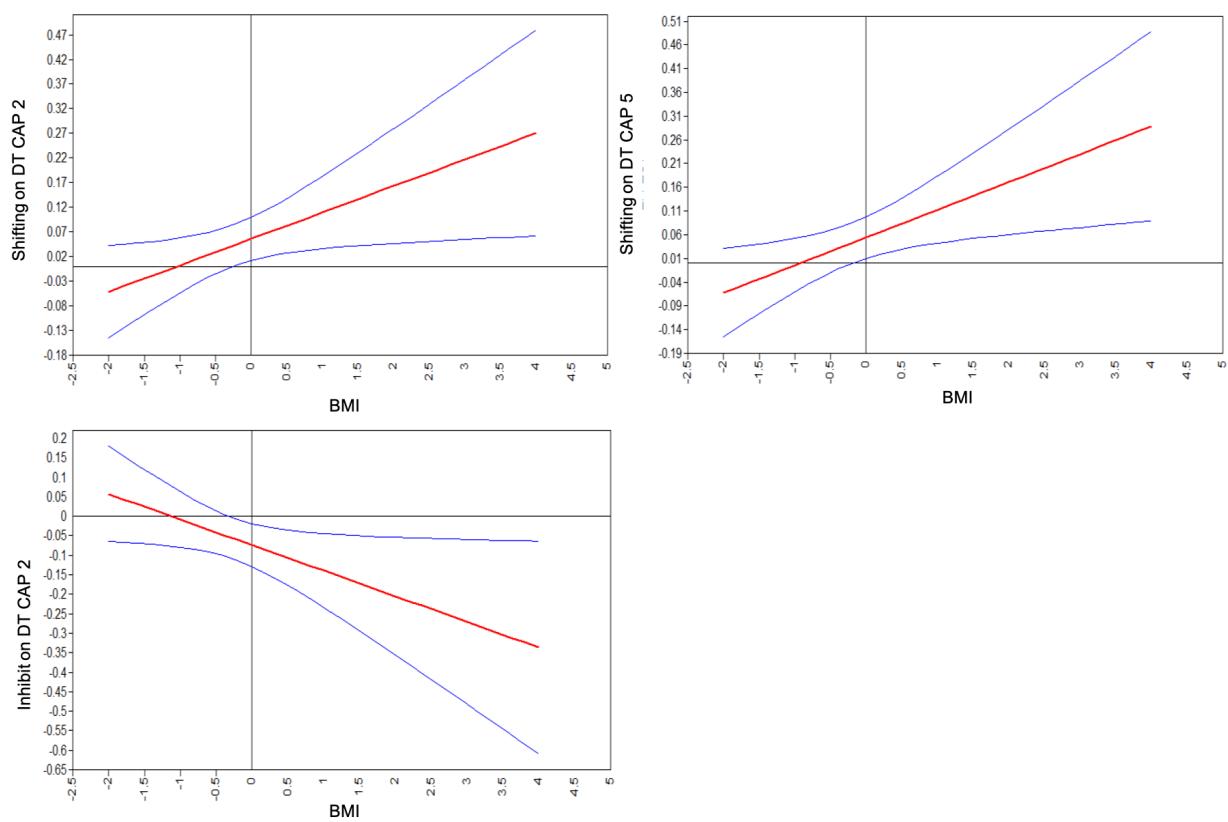


Figure S4. Johnson-Neyman Plots

Figure S5

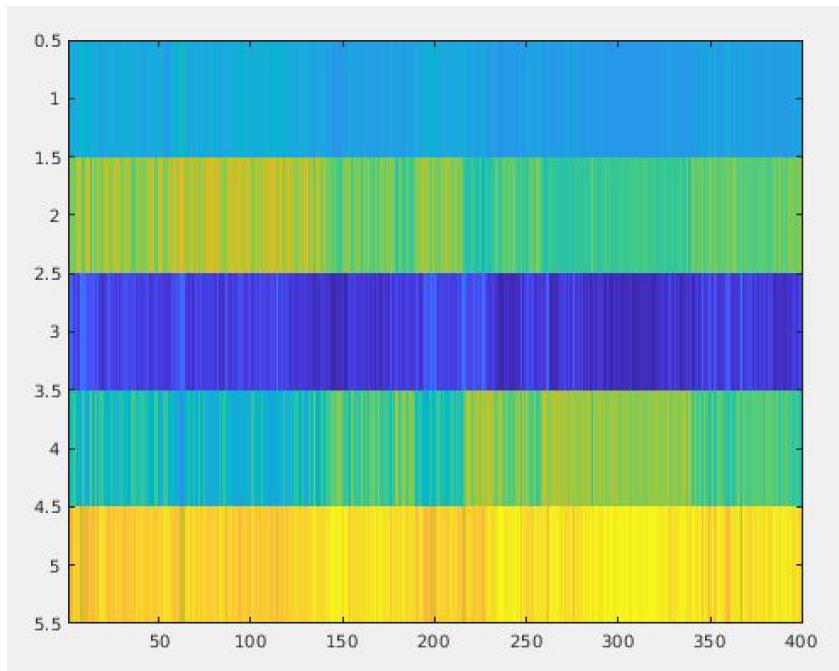


Figure S5. Co-activation pattern without global signal regression

Figure S6

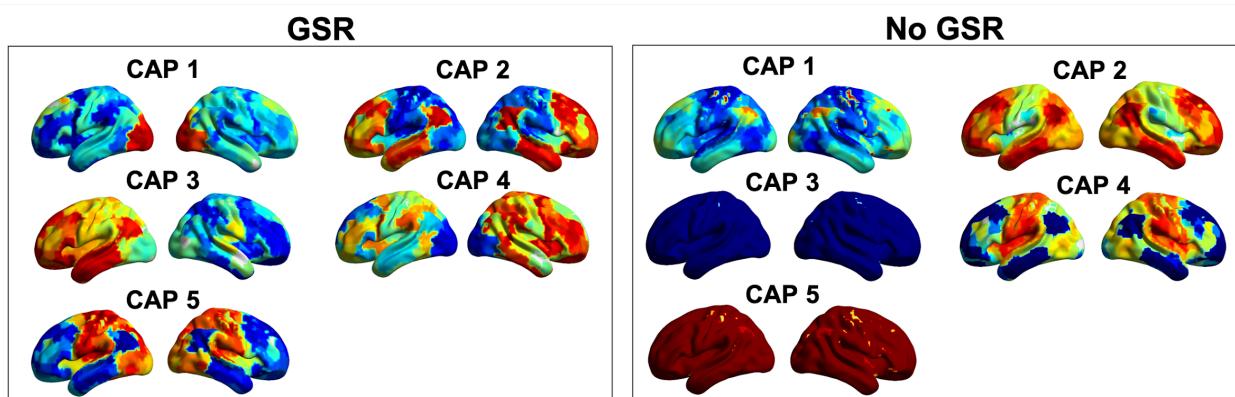


Figure S6. Co-activation patterns with global signal regression (GSR) and without global signal regression

Figure S7. Tests of Assumptions

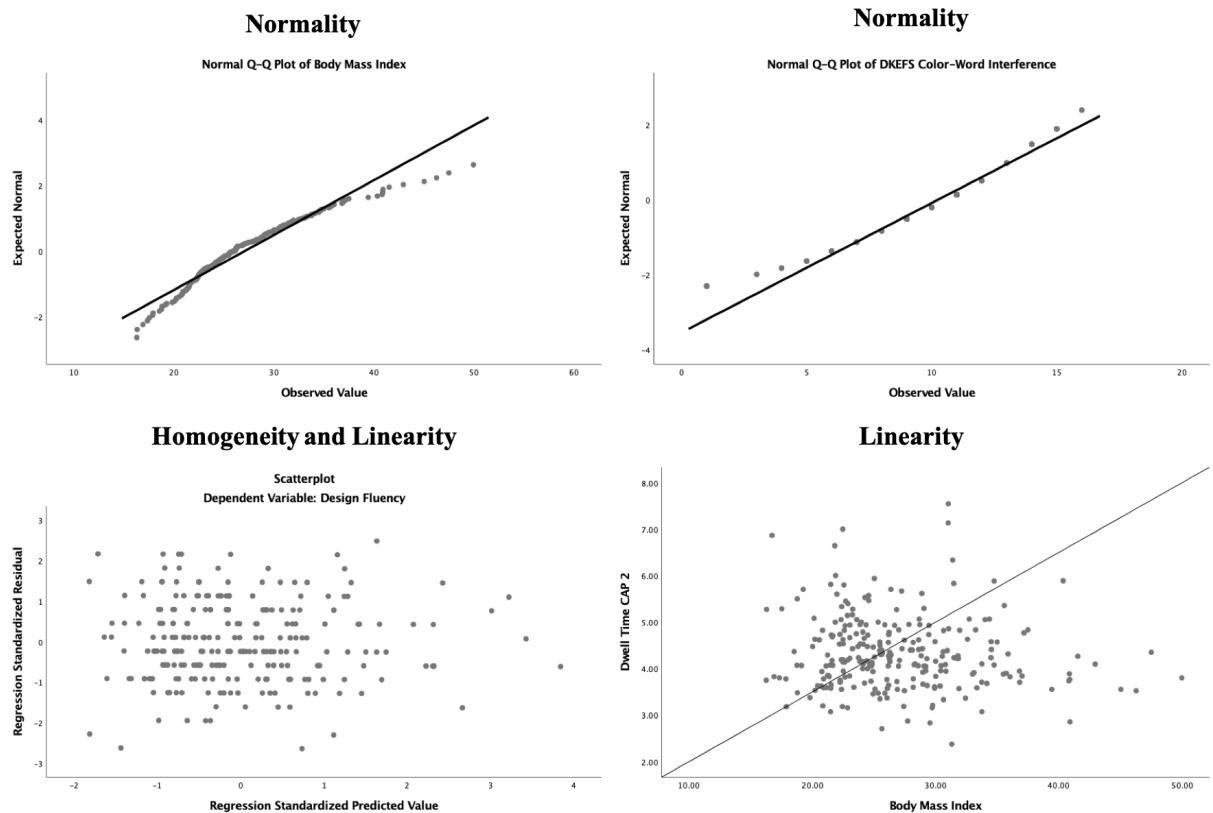


Figure S7.

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.

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	44.65 (21)	.002	.96	.05	.07

and shifting

* $p > .05$

Table S2. Summary of Simple Slopes Analysis

<i>Unstandardized</i>	<i>b</i>	<i>SE</i>
Shifting		
BMI x DT CAP 2 (-1 SD)	-0.04	0.15
BMI x DT CAP 2 (+1 SD)	0.06	0.15
BMI x DT CAP 2 (-2 SD)	-0.10	0.15
BMI x DT CAP 2 (+2 SD)	0.11	0.15
BMI x DT CAP 2 (-3 SD)	-0.16	0.16
BMI x DT CAP 2 (+ 3 SD)	0.17	0.16
BMI x DT CAP 5 (-1 SD)	-0.13	0.15
BMI x DT CAP 5 (+1 SD)	-0.02	0.14
BMI x DT CAP 5 (-2 SD)	-0.19	0.16
BMI x DT CAP 5 (+2 SD)	0.04	0.15
BMI x DT CAP 5 (-3 SD)	-0.25	0.17
BMI x DT CAP 5 (+ 3 SD)	0.10	0.15

BMI x Transitions (-1 SD)	0.01	0.01
BMI x Transitions (+1 SD)	0.001	0.01
BMI x Transitions (-2 SD)	0.01	0.01
BMI x Transitions (+2 SD)	-0.002	0.01
BMI x Transitions (-3 SD)	0.01	0.01
BMI x Transitions (+3 SD)	-0.01	0.01
<hr/>		
Inhibition		
<hr/>		
BMI x DT CAP 2 (-1 SD)	0.20	0.19
BMI x DT CAP 2 (+1 SD)	0.07	0.20
BMI x DT CAP 2 (-2 SD)	0.27	0.20
BMI x DT CAP 2 (+2 SD)	0.01	0.21
BMI x DT CAP 2 (-3 SD)	0.34	0.21
BMI x DT CAP 2 (+ 3 SD)	-0.06	0.22
BMI x DT CAP 5 (-1 SD)	0.10	0.19
BMI x DT CAP 5 (+1 SD)	-0.01	0.18
BMI x DT CAP 5 (-2 SD)	0.04	0.18

BMI x DT CAP 5 (+2 SD)	-0.07	0.19
BMI x DT CAP 5 (-3 SD)	0.21	0.21
BMI x DT CAP 5 (+ 3 SD)	-0.12	0.20
<hr/>		
Fluency		
BMI x DT CAP 4 (-1 SD)	-0.15	0.19
BMI x DT CAP 4 (+1 SD)	-0.05	0.18
BMI x DT CAP 4 (-2 SD)	-0.26	0.21
BMI x DT CAP 4 (+2 SD)	0.05	0.19
BMI x DT CAP 4 (-3 SD)	-.26	0.21
BMI x DT CAP 4 (+ 3 SD)	0.05	0.19
<hr/>		

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

Table S3. Frequency of occurrence of each co-activation pattern (CAP)

	Percentage % (SD)
CAP 1	19.36 (0.04)
CAP 2	19.29 (0.04)
CAP 3	18.60 (0.04)
CAP 4	23.39 (0.04)
CAP 5	19.35 (0.04)

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

	β	<i>b</i>	<i>SE</i>	<i>p</i>	95% CI
[lower 2.5%, upper 2.5%]					
Shift					
DT CAP 1	-.04	-.11	0.18	.548	[-0.45, 0.24]
DT CAP 3	.06	0.17	0.17	.319	[-0.17, 0.51]
DT CAP 4	-.02	-0.06	0.17	.708	[-0.39, 0.26]
F CAP 1	-.08	-3.90	2.77	.160	[-9.33, 1.53]
F CAP 2	-.002	-0.12	2.82	.967	[-5.65, 5.41]
F CAP 3	.06	2.97	3.00	.321	[-2.90, 8.85]
F CAP 4	.002	0.13	2.86	.965	[-5.48, 5.73]
F CAP 5	.03	1.46	2.89	.613	[-4.20, 7.12]
BMI	.13	0.04	0.02	.046*	[0.001, 0.09]
Age	-.07	-0.02	0.02	.210	[-.05, 0.01]
Mean FD	-.04	-0.95	1.49	.523	[-3.86, 1.96]
Sex	.18	0.72	0.23	.001**	[0.28, 1.16]
Inhibition					
DT CAP 1	-.24	-0.83	0.41	.044*	[-1.64, -0.02]
DT CAP 3	-.06	-0.24	0.43	.585	[-1.08, 0.61]
DT CAP 4	-.03	-0.09	0.44	.842	[-0.94, 0.77]

DT CAP 5	-.03	-0.09	0.37	.800	[-0.81, 0.63]
F CAP 1	.01	-0.54	3.52	.878	[-6.36, 7.44]
F CAP 2	-.01	-0.73	3.66	.841	[-7.91, 6.45]
F CAP 3	-.03	-1.82	3.92	.643	[-9.50, 5.87]
F CAP 4	.05	3.44	3.65	.345	[-3.71, 10.59]
F CAP 5	-.03	-1.69	3.63	.641	[-8.80, 5.41]
Transitions	-.17	-0.04	0.04	.264	[-0.11, 0.03]
BMI	-.15	-0.06	0.03	.025*	[-0.12, -0.01]
Age	.14	0.05	0.02	.013*	[0.01, 0.08]
Mean FD	-.03	-0.73	1.89	.699	[-4.43, 2.97]
Sex	-.07	-0.35	0.28	.211	[0.01, 0.08]

Fluency					
DT CAP 1	.003	0.01	0.36	.981	[-0.70, 0.71]
DT CAP 2	-.13	-0.30	0.28	.284	[-0.86, 0.25]
DT CAP 3	.03	0.08	0.39	.846	[-0.69, 0.84]
DT CAP 4	-.21	-0.51	0.29	.193	[-0.51, 0.10]
DT CAP 5	-.05	-0.13	0.33	.701	[-0.77, 0.52]
F CAP 1	-.01	-0.23	3.16	.942	[-6.43, 5.96]
F CAP 2	.09	4.24	3.25	.191	[-2.12, 10.60]
F CAP 3	-.09	-4.59	3.58	.200	[-11.61, 2.43]
F CAP 4	-.04	-2.07	3.24	.522	[-8.42, 4.27]
F CAP 5	.03	1.52	3.30	.646	[-4.96, 7.99]
Transitions	-.13	-0.02	0.04	.551	[-0.10, 0.05]
BMI	.01	0.004	0.03	.865	[-0.05, 0.05]
Age	-.02	-0.01	0.02	.746	[-0.04, 0.03]

Mean FD	.02	0.36	1.71	.835	[-2.99, 3.70]
Sex	-.06	0-0.22	0.26	.387	[-0.73, 0.28]

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

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