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ORIGINAL ARTICLE

Role of massa intermedia in human neurocognitive processing

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Abstract

Massa intermedia (MI) is an inconsistent midline structure in the human brain that is absent in approximately 30% of the population. Absence of MI is seen more frequently in schizophrenia spectrum disorder and bipolar disorder. However, very little is known about the normal role of MI in the human brain. The purpose of this study was to investigate the role of human MI in cortical and subcortical cognitive processing as determined by differences between subjects with and without MI. Using the Human Connectome Project database, a cohort of randomly selected participants were selected to (1) identify presence, absence, and size of MI, and (2) explore possible cognitive process mediated by the presence of MI. Four hundred and two brains were included (216 females) in the final analysis. Four independent blind raters identified 360 brains with MI (202 females) and 42 without MI using anatomical T1-weighted MR scans. Presence of MI was significantly more prevalent in female participant ($p = 0.005$) and they had significantly larger size of MI ($p = 0.001$ and 0.000 for anteroposterior and craniocaudal dimensions, respectively). There were no statistically significant differences in the presence of MI with regards to age, race and ethnicity. Further analysis revealed gender, flanker test, and loneliness as predictor of the presence of MI in a Firth logistic regression model ($p = 0.0004$). This is the largest study of human MI to date. MI may contribute to inter-hemispheric cortical and subcortical connectivity with resulting subtle neuropsychological differences among individuals with a present versus absent MI.

Keywords Massa intermedia · Interthalamic adhesion · Healthy human · Cognition · Sexual dimorphism

Introduction

The massa intermedia (MI), also known as the interthalamic adhesion, is an inconsistent midline structure that is absent in as much as 20–30% of the population (Malobabic et al. 1987; Trzesniak et al. 2011). Its function is poorly understood in the human brain (Frauceiger 1959). A large cadaveric study of brains across various decades of life suggested that MI atrophies and disappears altogether as a function of general brain atrophy (Rosales et al. 1968). Another study suggested that male subjects with MI had lower scores on the nonverbal performance tasks of the Wechsler–Bellevue Intelligence Scale compared with males without MI (Lansdell and Davie 1972). More recently, a neuroimaging and behavioral study explored the presence and size of MI and its correlation with neurocognitive function in the normal human brain. Damle and colleagues (2017) found that, in female participants, the size of MI positively mediated the relationship between age and the signal detectability index (“d prime”) of the Continuous Performance Test–Identical Pairs (CPT-IP), a measure of attention and vigilance.

Previous work by our group revealed the crossing of limbic fibers through MI, connecting the habenular region to the prefrontal cortex (Kochanski et al. 2018). In conjunction with demographic studies linking MI with psychiatric dysfunction, there is further evidence implicating MI interthalamic connectivity to the habenula and limbic system. MI is less prevalent and shorter in size among persons with schizophrenia-spectrum disorders compared to healthy controls (Takahashi et al. 2008b). Absence of MI has also been

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reported more frequently in individuals with bipolar disorder (Aine et al. 2017; Allen and Gorski 1991; Nopoulos et al. 2001; Snyder et al. 1998; Takahashi et al. 2008a; Trzesniak et al. 2011). Moreover, among epilepsy patients, subjects without MI performed worse on tests of verbal memory and executive function (Trzesniak et al. 2016). Thus, there is accruing evidence to suggest MI may be another midline commissure with neurocognitive contribution (Kochanski et al. 2018) that may augment subcortical and frontal systems function. It is curious, therefore, that MI is entirely absent in nearly a quarter of healthy humans.

The purpose of this exploratory study was to identify neuropsychological abilities that may be mediated by the presence or absence of MI in the human brain. We were particularly interested in exploring functions mediated by the limbic system and other frontal-subcortical structures (i.e., memory, emotion, olfaction, processing speed, motor abilities, and executive function), considering potential differences in age, sex, and handedness. To that end, we analyzed neuroimaging data in conjunction with cognitive, emotional, and motor measures from healthy unrelated subjects who participated in The Human Connectome Project (HCP), a large-scale neuroimaging research study. The aim of this study was to assess whether significant differences exist between individuals that do and do not have MI on neuropsychological measures.

Methods

Subjects

The Human Connectome Project research sample consists of 1206 subjects who are young healthy individuals with no known psychological or neurological disorders. Each subject underwent acquisition of multiple MRI sequences and a neuropsychological evaluation (Van Essen et al. 2013). Each participant was recruited with sibling(s), if available. For purposes of this study, one member of each family was randomly selected to avoid the potential confounding effect of shared familial genetics on brain structure and function. All subjects with an anatomical MRI scan were then included in our study. This resulted in a total of 413 brains (mean age = 28.9 ± 3.7 with 220 females and 193 males) included for analysis. The present study was reviewed and deemed exempt from Institutional Review Board oversight.

MI identification and measurement

Customized Siemens 3 T Skyra scanner used in HCP produced high-resolution anatomical images with 0.7 mm isotropic slices. 3D MPRAGE protocol was used with TR:2400 ms, TE:2.14 ms, TI:1000 ms and a flip angle of 8 degrees and field of view of 224 × 224 mm. T1 acquisition took 7 min and 40 s. In the preprocessing step, T1-weighted MR images were registered to MNI 152 standard template and aligned with the anterior–posterior commissure (AC-PC) plane. Detailed imaging parameters and preprocessing steps have been previously described (Glasser et al. 2013). Four raters blinded to the study aims independently reviewed the images and identified the presence or absence of MI (Fig. 1). A standardized technique was employed by all raters by way of examining all three dimensions of T1-weighted images (i.e., axial, as well as coronal and sagittal reconstructions). Slices depicting the midpoint of the third ventricle in the craniocaudal and anteroposterior dimensions were identified. MI presence was confirmed if definite non-fluid intensity was identified in the midline plane with bilateral connections to both thalami. Anteroposterior dimensions of MI were measured by identifying the axial slice with the longest measurement of MI. The longest craniocaudal dimensions were then measured on coronal plane in a similar fashion. All measurements were done using measure tool in *freeview* available in freesurfer suite.

Neuropsychological evaluation

Neuropsychological variables from the NIH Toolbox and additional neurobehavioral measures were included in the HCP data set. The NIH toolbox is a comprehensive set of tests evaluating motor, sensory, cognitive and emotional functions (Gershon et al. 2013; Weintraub et al. 2013). The assessment variables have been described extensively elsewhere (Barch et al. 2013) and a complete list of behavioral variables measured in the HCP study is available online (https://wiki.humanconnectome.org/download/attachments/53444663/HCP_S1200_DataDictionary_April_20_2018.xlsx). Based on the literature and our previous study (Damle et al. 2017; Kochanski et al. 2018; Lansdell and Davie 1972; Trzesniak et al. 2011), we incorporated demographic, neuropsychological, and behavioral variables encompassing the domains of cognition, motor, and sensory function, personality, and psychiatric history.

Statistical analysis

The analysis started with a pool of 141 neuropsychological and neurobehavioral variables of interest (see appendix 1 and 'https://wiki.humanconnectome.org/download/attachments/53444663/HCP_S1200_DataDictionary_April_20_2018.xlsx' for a full list of used variables and their definitions). To identify the most pertinent variables, the analysis was designed to consist two stages: (1) an initial data screen and (2) a prediction model building stage (see Ranganathan et al. 2017 for a detailed explanation of this methodology). Briefly, to have a more robust regression

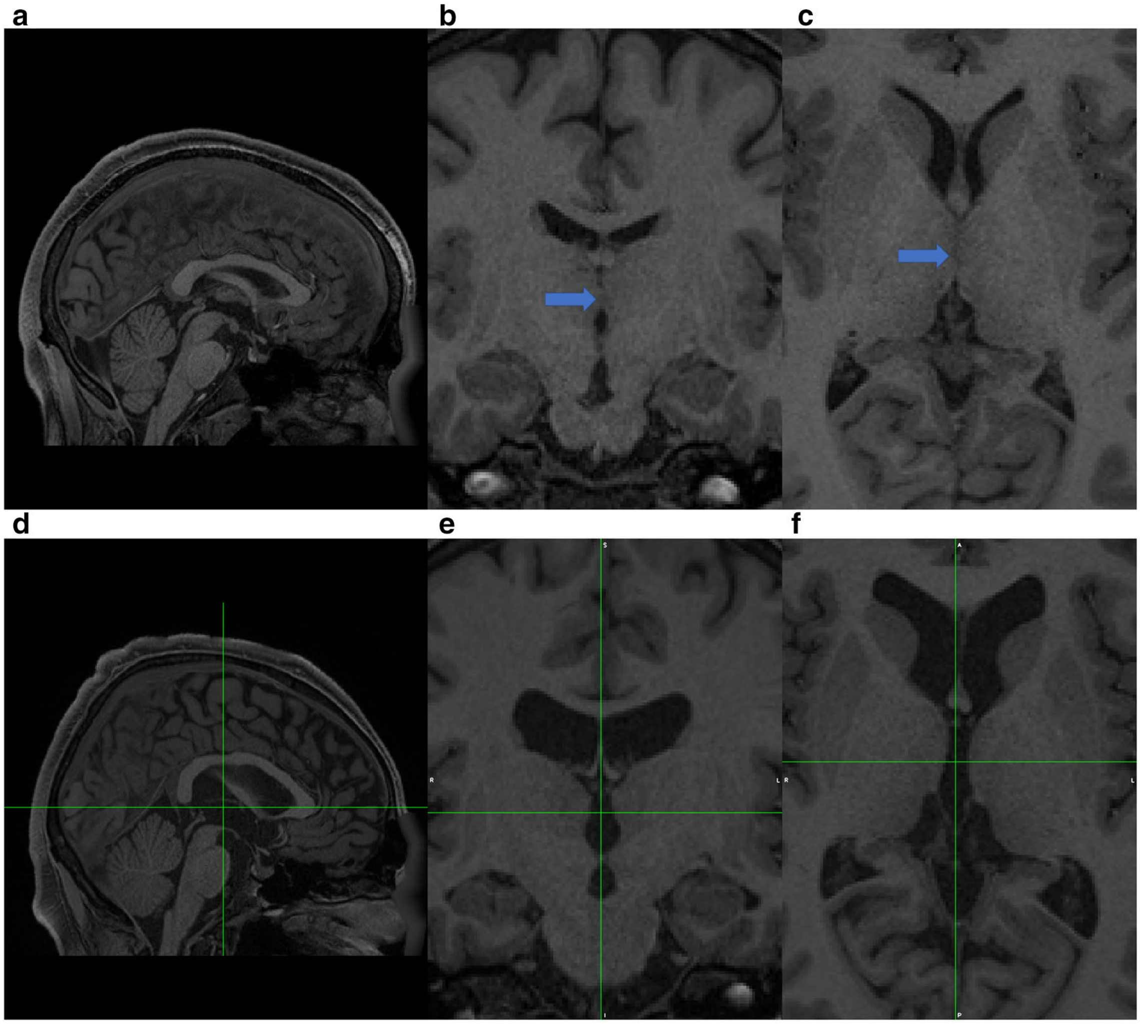

Fig. 1 T1-weighted MRI images of the third ventricle showing presence, *b* and *c* (coronal and axial, respectively), and absence, *e* and *f* (coronal and axial, respectively) of MI (arrow) as a midline structure connecting the two thalami. Sagittal views (**a**, **d**) are provided for proper anatomical orientation

model, first, univariate analysis are performed on all available variables with a more liberal cut-off for *p* values, i.e. 0.1 instead of 0.05, and then incorporating the chosen variables into the regression models). Essentially, in the first stage, liberal statistical criteria were used to eliminate variables with no apparent association with MI function. In the second stage, a data-driven modeling approach is used to further determine which of the remaining variables are the most strongly predictive of MI presence.

Initial data screening

In the first stage, the sample was divided into persons with and without MI. One hundred forty-one variables from the NIH Toolbox and additional neurobehavioral measures from the HCP dataset were selected for comparison. Between-group comparisons were evaluated by independent samples *t* tests for normally distributed variables, Mann–Whitney *U* tests for non-normally distributed variables, and Chi-square tests for categorical variables (see appendix 1 for details on distribution of the variables). Variables that were statistically different between the groups based on a liberal cut-off criterion (i.e., $p < 0.10$) were selected for further evaluation in the next stage.

Prediction modeling

In the second stage, the selected variables were entered into a statistical model to compare the relative power of each one to predict presence or absence of MI. Firth logistic regression was used for this purpose because of the relatively small number of subjects without MI. This method has been shown to give robust outcomes under similar data conditions (Allison 2012; Leitgöb 2013). Age, sex, and handedness were entered into the model along with the selected variables from the first stage. The analysis then proceeded iteratively in a backward stepwise regression approach. That is, non-significant variables were excluded one by one from the regression equation in each step. The final model was statistically significant and included only significant predictors. The false discovery rate correction (Benjamini and Hochberg 1995) was used to address the issue of multiple comparisons across each backward step. All statistical analyses were conducted using SPSS Version 25 integrated with R. Firth logistic regression was run using the 'logistf' package (Dunkler et al. 2018).

Results

Eleven brains were excluded from the initial 413 due to the inability in differentiating between the presence or absence of MI (i.e. kissing thalami versus presence of MI **appendix 2**). Out of the remaining 402 brains included (216 females) in the study, 360 were identified as having MI (202 females and 158 males). Presence of MI was significantly more common in females than males ($\chi^2=7.849$, $df=1$, $p=0.005$). There were no statistical differences between the two groups with regard to age ($t=0.274$, $p=0.784$), handedness ($t=0.450$, $p=0.653$), race ($\chi^2=6.626$, $df=4$, $p=0.157$) and ethnicity ($\chi^2=1.003$, $df=2$, $p=0.606$) (Table 1).

Table 1 Demographic information of subjects

	MI	No MI	*p* value
Age (SD)	28.8 (3.7)	29 (3.5)	0.784[a]
Sex (*n*)			
Female	202	14	0.005[b]
Male	158	28	
Handedness[c] (SD)	64.2 (45.1)	67.5 (42.6)	0.653[a]
Race (*n*)			0.157[b]
Asian/Native Hawaiian/ Other Pacific Islander	29	2	
Black or African American	54	3	
White	61	8	
More than one	265	33	
Unknown or not reported	4	2	
Ethnicity (n)			0.606[b]
Hispanic/Latino	33	5	
Not Hispanic/Latino	321	37	
Unknown or not reported	6	0	

Women were found to have MI more prevalent than men. *MI* = Massa Intermedia (Present $n=360$; Absent $n=42$)

[a]Student *t* test

[b]Pearson Chi square

[c]Edinburgh Handedness Inventory

Among subjects with MI, females had significantly larger MI dimensions when the anteroposterior ($t=3.510$, $p=0.001$) and craniocaudal ($t=4.432$, $p=0.000$) dimensions were analyzed (Table 2). Age was not significantly associated with MI size. Analysis of MI size in relation to the aforementioned neuropsychological metrics found that grip strength 'strength' was negatively correlated with the both dimensions of MI ($\rho=-0.151$, -0.22, $p=0.004$, 0.020 for craniocaudal and anteroposterior dimensions, respectively) while Flanker executive function test 'Flanker' was negatively correlated with craniocaudal dimension of MI only ($\rho=-0.120$, $p=0.022$). On the other hand, Taste Intensity Test 'taste' was positively correlated with both dimensions of MI ($\rho=0.176$, 0.192, $p=0.001$, 0.000 for craniocaudal and anteroposterior dimensions, respectively).

In the first analytic stage, 17 variables initially met criteria for inclusion into the regression equation**.** These variables included total number of correct responses in Penn Word Memory Test 'IWRD_TOT' ($U=8847.000$, $p=0.042$), 9-hole Pegboard Dexterity Test 'Dexterity' ($t=1.985$, $p=0.048$), Openness scale score 'NEOFAC_O' (Digman 1990) ($t=-2.066$, $p=0.039$), Taste ($t=2.044$, $p=0.042$), NIH toolbox self-reported loneliness 'loneliness' ($t=-2.593$, $p=0.010$) and six scores of the Achenbach adult self-report, syndrome scales and DSM-oriented scale 'ASR_DSM' (Achenbach et al. 2003) including: withdrawn 'ASR_Witd' ($U=5969.500$, $p=0.030$), rule braking behavior 'ASR_Rule' ($U=5756.500$, $p=0.013$), other problems 'ASR_Oth' ($U=6049.500$, $p=0.043$), critical items 'ASR_Crit' ($U=5879.00$, $p=0.023$), sum of scale IV, V and other 'ASR_TAO'($U=5877.500$, $p=0.023$), total score 'ASR_Totp' ($U=5945.000$, $p=0.030$) and DSM avoidant personality problems 'DSM_Avoid' ($U=5747.500$, $p=0.013$). Five test scores were marginally statistically different between the two groups (i.e. $p<0.10$): Flanker ($t=1.719$, $p=0.087$), strength ($U=6174.500$, $p=0.052$), fluid cognition composite score 'CofFluidComp' ($t=1.739$, $p=0.083$), NIH toolbox

Table 2 MI size as determined by anterior–posterior and craniocaudal measurements and stratified by sex

	Anteroposterior (mean in mm)	*p* value	Craniocaudal (mean in mm)	*p* value
All	14.61 ± 2.8		10.47 ± 2	
Female	15.07 ± 2.54	0.001[a]	10.89 ± 1.79	0.000[a]
Male	14.02 ± 2.98		9.9 ± 2.14	
Strength	$\rho=-0.22$	0.020	$\rho=-0.151$	0.004
Flanker	$\rho=-0.065$	0.216	$\rho=-0.120$	0.022
Taste	$\rho=0.192$	0.000	$\rho=0.176$	0.001

Statistically different MI size-correlated neuropsychologic measures are detailed as well

[a]Student's *t* test and *ρ* Pearson correlation coefficient

self-reported positive affect 'PosAffect' ($U = 8727.500$, $p = 0.093$) and ASR-DSM thought problems 'ASR_Thot' ($U = 6299.500$, $p = 0.089$). Participants without MI scored higher (worse) in ASR_DSM measures and had higher scores in loneliness (feeling lonelier), NEOFAC_O, and strength. Presence of MI was, on the other hand, associated with higher scores in IWRD_TOT, Dexterity, Taste, CogFluidComp, PosAffect and Flanker. Upon further evaluation, ASR_DSM variables evidenced high inter-correlation coefficients (i.e., $r > 0.700$). Four of these variables were dropped moving forward to minimize multicollinearity and avoid redundancy (i.e., ASR_Crit, ASR_Totp, ASR_TAO, DSM_Avoid). Thus, a total of 13 behavioral variables (Table 3) and sex were included in the second analytic stage.

Prediction model

The final model (please see appendix 3 for iteration of all models) was significant (LRT = 18.07, $df = 3$, $p = 0.00042$) and consisted of three predictors: (1) sex ($\beta = 0.953$, $p = 0.004$), (2) flanker task ($\beta = 0.032$, $p = 0.040$), and (3) loneliness ($\beta = -0.049$, $p = 0.010$). The correlation between loneliness and the flanker test was non-significant ($r = 0.049$, $p = 0.328$). Males and females did not differ significantly on the flanker task ($t = 1.888$, $p = 0.060$, male mean = 111.95, SD = 11.22 versus female mean = 109.99, SD = 9.35) or levels of loneliness ($t = 0.412$, $p = 0.680$, male mean = 51.24, SD = 9.06 versus female mean = 50.88, SD = 7.89).

Table 3 Comparison of mean neuropsychological performances

	Mean (SD)		
	MI	No MI	*p* value
Penn word memory test	36 (3)	35 (3)	0.042[a*]
9-hole Pegboard dexterity test	112 (10)	109 (11)	0.048[b*]
Taste	96 (15)	91 (11)	0.042[b*]
loneliness	51 (8)	54 (8)	0.01[b*]
ASR-DSM withdrawn	2.2 (2.3)	2.9 (2.35)	0.03[a*]
ASR-DSM rule braking behavior	2.5 (2.7)	3.6 (2.94)	0.013[a*]
ASR-DSM other problems	9.2 (4.47)	10.2 (3.77)	0.043[a*]
Flanker	111 (10)	108 (10)	0.087[b]
strength	116 (11)	120 (12)	0.052[b]
Fluid cognition composite score	115 (11)	111 (10)	0.083[b]
NIH toolbox self-reported positive affect	51 (8)	48.7 (7.8)	0.093[a]
ASR-DSM thought problems	2.1 (2.17)	2.6 (1.95)	0.089[a]

Statistically significant differences were seen in the 9-Hole Pegboard Test, List Sorting Test, and Processing Speed tests. MI = Massa Intermedia (present $n = 360$; absent $n = 42$)

[a]Mann–Whitney *U* test

[b]Student's *t* test; $^{*}p < 0.05$

Discussion

Minimal empirical work has been published on the functional role of MI. Through a data-driven exploratory process, we were able to identify variables that suggest MI may play a role in negative emotional function (i.e., loneliness) and inhibition and attention (i.e., flanker task) among healthy adult humans. The correlation between the flanker task and loneliness was not significant and scores on these measures did not differ by sex. This suggests that each of the three identified variables predict unique variance in human MI function.

Our statistical analysis used an exploratory, two-stage, data-driven methodology with some theoretical constraints to identify variables related to limbic system and frontal-subcortical functions (e.g., homeostasis, olfaction, memory, emotion, processing speed, executive function, and attention). However, we did not make strong a priori predictions about specific variables in the HCP dataset related to MI faculty. The studies that are available have implicated MI in neuropsychiatric disorders (Hirayasu and Wada 1992; Nopoulos et al. 2001; Takahashi et al. 2008b; Trzesniak et al. 2011), attention (Damle et al. 2017), nonverbal IQ (Lansdell and Davie 1972), verbal memory and executive function (Trzesniak et al. 2016), and limbic system functional connectivity (Kochanski et al. 2018). Thus, we initially selected a broad range of 141 variables from the HCP dataset related to the cognitive, motor, sensory, and psychiatric aspects of limbic system and frontal-subcortical function. Firth logistic regression was used in a backward stepwise selection approach to identify the variables that best predicted the presence or absence of MI. This methodology has been shown to provide less biased results compared to standard logistic regression in the context of predicting rare events, i.e. prevalence of absence of MI in our cohort (Cole et al. 2013; Firth 1993; King and Zeng 2001). Below, the possible relationship between MI and each of the three identified predictors are discussed.

Sex difference

Females were more likely to have MI, whereas males were more likely to be missing MI. These findings are consistent with multiple studies on sex and the incidence of MI (Allen and Gorski 1991; Malobabić et al. 1987; Nopoulos et al. 2001; Samra and Cooper 1968). The functional implications of this difference are unclear. In a meta-analysis of 11 studies on MI and psychosis, both females and males without MI were shown to have greater rates of schizophrenia spectrum disorders compared to healthy controls; however, the effect sizes did not differ significantly between the sexes even though the incidence of MI presence did differ (Trzesniak et al., 2011). To our knowledge, this is the first study to show a significant MI-related sexual dimorphism in healthy humans.

Loneliness

Loneliness has been described as the perception of social isolation (Cacioppo et al. 2014). In this definition, perception is the critical component. That is, loneliness is a distinct concept from introversion (i.e., a characteristic preference for low levels of social interaction) and is not dependent on the number of social contacts a person may have (i.e., it is possible to feel lonely in a crowd). Over the past 30 years, loneliness has emerged as a critical risk factor for morbidity and mortality (House et al. 1988). For example, loneliness was found to be a greater risk factor for mortality compared to obesity and air pollution in a meta-analytic study (Holt-Lunstad et al. 2010). Loneliness also has important implications for cognition. For example, loneliness was found to be an important predictor of cognitive decline in a longitudinal aging cohort study of 823 older adults (Wilson et al. 2007).

The NIH Toolbox Loneliness Survey (Cyranowski et al. 2013) is a five-item Likert scale that prompts the respondent to rate the frequency of lonely feelings over the past month (e.g., "I feel left out"). The measure has demonstrated excellent reliability (Cronbach's $\alpha > 0.90$) and appeared to be a valid measure in a study of suicidal ideation (Klim et al. 2019). In our study, persons without MI endorsed greater levels of loneliness.

The possible contribution of MI in the perception of loneliness may be related to ventral striatum function. In a diffusion tensor imaging study by Kochanski and colleagues (2018), stria medullaris thalami (SM) fibers were identified in the MI. SM is thought to be part of a "negative emotion processing" circuit that includes the lateral habenula, anterior cingulate region, anterior insula, and dorsal orbitofrontal cortex (Wang and Aghajanian 1977; Mirrione et al. 2014). This circuit may play a role in modulating the ventral striatum (Sartorius and Henn 2007; Sartorius et al. 2010). Loneliness has also been found to play a role in differential activation of the ventral striatum (Cacioppo et al. 2009). In this study by Cacioppo et al. (2009), scores on a loneliness measure were associated with activation in the ventral striatum in response to social and nonsocial visual stimulation (i.e., pleasant pictures of people and objects). Greater levels of loneliness were associated with lower levels of ventral striatum activation in response to pictures of people. Our finding that healthy persons without MI endorse greater levels of loneliness may suggest less efficient modulation of the ventral striatum and associated areas (e.g., the thalamus, amygdala, and insula). Future studies are necessary to determine the reliability of the finding that the presence of MI may be predicted by levels of loneliness. An interesting future hypothesis would be to determine whether age-related involution and loss of MI across the lifespan, if it does indeed occur, is associated with changes in loneliness.

Inhibition

Flanker tasks are a class of tests of inhibition based on a paradigm developed by Eriksen and Eriksen (1974). The specific flanker task included in the NIH Cognitive Toolbox (Weintraub et al. 2013) involves presenting the respondent with a line of arrows on a computer screen. The respondent must focus on the central arrow, while ignoring the arrows flanking it and then press one of two keys to indicate whether the arrow is pointing left or right. In the congruent condition, the flanking arrows are pointing in the same direction as the target arrow. In the incongruent condition, the flanking arrows are not uniform and each one may point in either the opposite or the same direction as the target. On this task, there are 40 trials and the resultant score is a combination of accuracy and reaction time. In our sample, this flanker task was found to be a significant predictor of presence of MI. Persons with MI performed better on the flanker task compared to those without MI.

The role of MI in inhibitory control is unclear. Inhibition is the cognitive ability to restrain, suppress, or ignore inappropriate or distracting thoughts and behaviors to carry out a task or complete a given goal (Logan 1985). Inhibition is typically described as both, one of many component abilities that comprise the executive functions (Burgess 1997; Miyake et al. 2000; Miyake and Friedman 2012) and as being an ability that is itself comprised of multiple subcomponents. Many cognitive models of inhibition have been proposed that delineate the various aspects of this construct (e.g., Chuderski et al. 2012; Dempster 1993; Friedman and Miyake 2004; Pettigrew and Martin 2014; Stahl et al. 2014; Rey-Mermet et al. 2018). Flanker tasks are thought to measure at least one aspect of inhibition, freedom from distraction by irrelevant stimuli (e.g., Rey-Mermet et al. 2019). One possibility involves the cingulum. The anterior cingulate cortex is frequently implicated in flanker tasks (Fan et al. 2005; Posner 2008). This structure, like the stria medullaris, feeds into the lateral habenula (Wang and Aghajanian 1977; Mirrione et al. 2014). Thus, it is possible that absence of MI results in inefficient processing in the anterior cingulate cortex when resolving conflict between incongruent visual stimuli.

Size of MI

We investigated the size of MI in mediating neuropsychological measures. Both anteroposterior and craniocaudal dimensions of MI were significantly larger in female subjects. Previous studies have provided variable results. While Damle and colleagues reported larger MI size in female participants (Damle et al. 2017), another study found males to have larger MI (Mohammadi et al. 2008). It is of note that the latter study found transverse dimension of MI to be larger in males as opposed to the former study which measured the overall size of MI. It is likely that inconsistencies in imaging technique, measuring technique as well as smaller sample sizes are responsible for variable results.

We also noted a larger MI being associated with higher taste intensity scores. Prior studies suggest taste processing is associated with activation of bilateral dorsomedial thalamus, bilateral anteroventral and middle dorsal insula and bilateral post-central gyrus (Yeung et al. 2017; Haase et al. 2007; Iannilli et al. 2012) further suggesting increased interhemispheric connections by way of MI may provide an advantage in taste processing.

MI size (both craniocaudal and anteroposterior dimensions) was negatively correlated with grip strength. The craniocaudal size of MI was also negatively correlated with flanker task scores. It is interesting to note, however, that while the craniocaudal size of MI was negatively correlated with flanker task scores, the presence of MI in the regression model was positively mediated by flanker scores. The reason for these findings is unclear but consideration should be given to technical limitations when measuring MI dimensions after image processing which can result in partial volume averaging.

Limitations

The authors acknowledge this exploratory study has limitations. First, the sample used in the study was derived from the HCP database which provides a wide range of neuropsychological, neuroanatomical, and psychiatric variables. This provides an extremely large set of variables to investigate, particularly in the context of limited available empirical literature on MI function in humans. As a result, we employed an exploratory, data-driven approach in which we vetted numerous plausible predictor variables. The potential hazard of such an approach with subsequent stepwise regression analysis is that the results may capitalize on chance and/or over-fit the model to the data. Consequently, the findings reported in this study should be considered preliminary and the conclusions somewhat speculative.

Second, while the entire repository of the human HCP database was searched, the study involved a relatively small sample size that yielded only 42 subjects without MI. To address this limitation, we employed Firth logistic regression to predict the rare event of MI absence. However, the need for larger sample sizes with greater numbers of subjects without MI is crucial to solidify findings of the current study.

Third, our study examined function in healthy adults of a limited age range. Some aspects of MI function may be subtle in this context. For example, differences in emotional processing may be difficult to detect between persons with and without MI using behavioral tests and questionnaires, as these functions may be well-compensated by other brain regions. This points to the need for (1) a larger sample size of normal subjects across various age groups and (2) evaluation of MI function in targeted neurocognitive and psychiatric disease states where functional differences may be more robust.

Conclusion

In this data-driven, exploratory analysis, we found that presence of MI is most strongly predicted by sex, loneliness, and inhibition. Age, handedness, race, and ethnicity were not predictor of MI presence. More research is needed to elucidate the functionality of this poorly understood structure.

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