Fluid intelligence is associated with cortical volume and white matter tract integrity within multiple-demand system across adult lifespan

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ABSTRACT

Background: Fluid intelligence (Gf) is the innate ability of an individual to respond to complex and unexpected situations. Although some studies have considered that the multiple-demand (MD) system of the brain was the biological foundation for Gf, further characterization of their relationships in the context of aging is limited. The present study hypothesized that the structural metrics of the MD system, including cortical thickness, cortical volumes, and white matter (WM) tract integrity, was the brain correlates for Gf across the adult life span. Partial correlation analysis was performed to investigate whether the MD system could still explain Gf independent of the age effect. Moreover, the partial correlations between Gf and left/right structural metrics within the MD regions were compared to test whether the correlations displayed distinct lateralization.

Methods: The participants were recruited from the Cambridge Centre for Ageing and Neuroscience (Cam-CAN) databank, comprising the images of 603 healthy participants aged 18–88 years acquired on a 3-T system. The MRI data included high-resolution T1-weighted and diffusion-weighted images, from which gray matter and WM structural metrics of the MD system were analyzed, respectively. The structural metrics of gray matter were quantified in terms of cortical volume/thickness of five pairs of cortical regions, and those of WM were quantified in terms of the mean axial diffusivity (DA), radial diffusivity (DR), mean diffusivity (DM), and generalized fractional anisotropy (GFA) on five pairs of tracts. Partial correlation controlling for age and sex effects, was performed to investigate the associations of Gf scores with the mean DA, DR, DM and GFA of all tracts in the MD system, those of left and right hemispheric tracts, and those of each tract. Fisher’s exact test was used to compare the partial correlations between left and right MD regions.

Results: The linear relationship between cortical volumes and Gf was evident across all levels of the MD system even after controlling for age and sex. For the WM integrity, diffusion indices including DA, DR, DM and GFA displayed linear relationships with Gf scores at various levels of the MD system. Among the 10 WM tracts connecting the MD regions, bilateral superior longitudinal fasciculus I and bilateral frontal aslant tracts exhibited the strongest and significant associations. Our results did not show significant inter-hemispheric differences in the associations between structural metrics of the MD system and Gf.

Conclusion: Our results demonstrate significant associations between Gf and both cortical volumes and tract integrity of the MD system across the adult lifespan in a population-based cohort. We found that the association remained significant in the entire adult lifespan despite simultaneous decline of Gf and the MD system. Our results suggest that the MD system might be a structural underpinning of Gf and support the fronto-parietal model of cognitive aging. However, we did not find hemispheric differences in the Gf-MD correlations, not supporting the hemi-aging hypothesis.

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1. Introduction

Real-life problem-solving skills require more than accumulated knowledge and information. Upon encountering novel situations, one must be able to effectively encode new information, accurately retrieve acquired concepts and knowledge, and formulate proper solutions. Previous research has indicated that fluid intelligence was related to the complex cognitive measures of induction, quantitative reasoning, visualization, and problem solving (Duncan et al., 2017). Raymond Cattell defined fluid reasoning as “the ability to discriminate and perceive relations between any fundamentals, new or old” (Cattell and Cattell, 1963). He extended Spearman’s general factor to fluid intelligence (Gf) and crystallized intelligence (Gc), and he constructed the nonverbal Culture Fair Intelligence Test to assess Gf (Cattell, 1963). For assessing Gf, nonverbal or abstract tests are often adopted to estimate perceptual organization factors of complex problem-solving tasks. High performance in these tests predicts a wide range of success in school performance and job career (Jensen, 1998).

Gf is related to general cognition, such as logical reasoning, working memory, and decision-making. Behavioral studies have explored cognitive attributes of Gf, and found that various fundamental working memory functions (i.e., spatial span, digit span, and visual short-term memory), and even more complex tasks are strongly associated with Gf (Ackerman et al., 2005; Duncan et al., 2012; Kane and Engle, 2002). Gf also exhibits strong associations with attention and executive control functions of the frontal lobe (Cole et al., 2015; Duncan, 1995; Unsworth et al., 2014). Based on the aforementioned associations, Duncan et al. (2017) elaborated that Gf may represent dynamic attentional control functions of the frontal and parietal cortices. These findings elaborated a person’s cognitive abilities underlying the complex mental ability of Gf and explained the reason why high performance on a Gf test could predict future success in educational and occupational career.

Human functional magnetic resonance imaging (MRI) studies have consistently found that many cognitive functions such as working memory, attention, numerical calculation and logic reasoning, and problem solving are processed by common brain regions (Duncan, 2010; Fedorenko et al., 2013; Naghavi and Nyberg, 2005); hence, the multiple-demand (MD) brain system (Duncan, 2010) has been proposed. The MD brain regions are located in the frontal and parietal lobes; the regions mainly involved posterior-lateral and dorso-medial aspects of the frontal lobe and middle part of the parietal lobe. Moreover, lesion studies examining Gf in patients with focal cortical lesions have supported the engagement of such a network-wise framework in Gf function and have found that Gf deficits correspond to the damage to specific regions confined to the frontal and parietal cortices (Barbey et al., 2014; Glascner et al., 2009; Woolgar et al., 2010). However, the age scope of the samples in most of the studies is relatively small and younger than 30 years. The nature of Gf in a broader age scope awaits further investigation.

Aging often comes along with brain atrophy and senescence of cognitive functions, such as memory and executive functions (Murman, 2015). There are two contemporary theories of cognitive aging based on neuropsychological evidence obtained from typically aging elderly: the frontal aging hypothesis (West, 1996) and the hemi-aging hypothesis (Goldstein and Shelly, 1981). The frontal aging hypothesis claims that aging-related deterioration of cognition is attributed to the atrophy of the prefrontal cortex more than other brain regions (Gazzaniga, 1995). The frontal aging theory has been widely acknowledged because its support is accumulating evidence relating the senescence of cognitive functions, including attention and executive functions or more specific tasks such as psychomotor speed and free memory retrieval, to the loss of cortical volume mainly in the prefrontal cortex, dorsal thalamus, and the frontal white matter (WM) tracts such as anterior part of the corpus callosum and the anterior thalamic radiations (Fjell et al., 2009a; b; Head et al., 2005; Landau et al., 2011; Raz et al., 2010; Seidler et al., 2010; Taconnat et al., 2007). Gawron et al. (2014) applied a comprehensive neuropsychological battery on a group of cognitively normal people aged greater than 80 years. The battery covered the main cognitive functions including attention, processing speed, memory, reasoning, executive control and visuospatial functions. By applying a hierarchical cluster analysis on participants’ cognitive profiles, they categorized the participants into four groups with different cognitive patterns: preservation of overall cognitive performance, decline of attention, impairment of executive control and prolongation of processing speed. They found that the first three groups were consistent with the dysfunction of the fronto-parietal circuit (Kennedy and Raz, 2009) and responsible for the senescence of complex cognitive functions. To date, however, neuroimaging evidence of the correlation between Gf and the MD system under the context of aging is still limited.

The hemi-aging hypothesis claims that typical aging affects nonverbal domains which are dominated by the right hemisphere more than the left-hemisphere (Goldstein and Shelly, 1981; Meudell and Greenhalgh, 1987). The hypothesis is supported by some neuropsychological reports and lesion studies (Dolcos et al., 2002; Glascner et al., 2009). For example, figural reasoning, which involves both analytic reasoning and spatial and object working memory, is associated with right frontal and parietal regions (Prabhakaran et al., 1997; Villardita, 1985). Because Gf is associated with nonverbal domains, right hemispheric lateralization may be the characteristic of Gf, it follows that there should be a lateralized pattern of Gf-MD relationships. To date, neuroimaging studies provide limited evidence for the hemi-aging hypothesis which claims the presence of hemispheric differences of the Gf-MD correlations throughout lifespan (Fjell et al., 2009a).

Therefore, the aim of the present study was to characterize the neural basis of Gf in terms of structural metrics of the MD system, including cortical thickness, cortical volume, and WM tract integrity. Specifically, we analyzed the relationships between Gf and structural metrics of the MD system in a large cohort of 603 healthy participants aged 18–88 years. We investigated whether age-related changes of the fronto-parietal neuropsychological model, specifically the MD system, could still explain Gf independent of the age effect. Moreover, we tested the hemi-aging hypothesis by examining lateralized patterns of Gf-MD relationships across the adult lifespan. The knowledge gained from this study could shed light on the structural underpinning of the brain that supports Gf.

2. Materials and methods

2.1. Participants

The participants were recruited from the Cambridge Centre for Ageing and Neuroscience (Cam-CAN) project (www.cam-can.com). A detailed description has been provided in the studies of Shafto et al. (2014) and Taylor et al. (2017). The East of England-Cambridge Central Research Ethics Committee (original the Cambridgeshire 2) approved the ethical approval for the study. After providing full informed consent, all participants underwent a diverse set of neuropsychological tests, conducted cognitive tasks, and received MRI scans. Participants were excluded if they had a low Mini-Mental State Examination (MMSE) score (24 or lower), poor fluency in English (non-native or nonbilingual English speakers), poor vision or hearing, self-reported substance abuse, and currently undergoing serious health problems. Participants who did not meet the safety and health-related criteria of MRI scanning were also excluded. A total of 603 participants aged 18–88 years were recruited in the study. Table 1 provides the demographic information of participants including age, sex, MMSE, and Gf scores.

2.2. Behavioral task

For the Gf task, the classification subtests of the standard Cattell Culture Fair Test were used, and the cognitive abilities measured by core cognitive process of Gf were evaluated (Duncan, 2010). The behavioral tasks were performed based on the references provided by Cam-CAN (Shafto et al., 2014; Taylor et al., 2017). The detailed information for
were necessary to spatially register an image to a template by local
elementary brain (Ashburner, 2007). DBM analyzed the deformations that
compartment and enabled completely automatic analysis across the
of gray matter within the predefined regions to individual subject space
(named region-based morphometry), and this allowed the overall values
of gray matter within the pre-defined regions to be estimated (Yotter
et al., 2011a, 2011b). Surface-based morphometry was applied to esti-
mate cortical thickness using CAT12 (Dahnke et al., 2012a; Yotter et al.,
2011c). Cortical volume and thickness indices were calculated for the MD
regions provided by the LONI LPBA40 atlas (http://www.loni.usc.edu/re-
search/atlas).

The MD system comprises specific brain regions in the frontal and
parietal lobes which are known to be activated when performing
demanding cognitive tasks (Fedorenko et al., 2013), and the damage to
which is associated with reduced Gf (Woolgar et al., 2010). We selected
the cortical MD regions reported by Duncan (2010) as the regions of
interest identified in the LONI LPBA40 atlas. In Duncan’s study (Duncan,
2010), the MD map was drawn from brain activation regions associated
with a wide range of cognitive functions, including working memory
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the standard protocol in Scale 2, Form A of Cattell Culture Fair test can be
found in other papers using the same dataset (Kievit et al., 2014), and De
Mooij et al. (2018). The optimal testing of Gf abilities such as pattern
recognition, abstract reasoning, and problem solving was assessed using
the factor analytic approach (Carroll, 1993; Cattel, 1971). The total
maximum scores of the Cattell Culture Fair tests were 46; the tests con-
sisted of three scales with nonverbal visual puzzles involving series
completion, odd-one-out, matrices, and topology within limited testing
time (Domino and Domino, 2006). The Gf using the standard protocol in
Scale 2, Form A of Cattell Culture Fair test, was assessed through the
pencil-and-paper method.

2.3. Image acquisition

All participants were scanned using a 3-T MRI scanner (TIM, Trio,
Siemens, Erlangen, Germany) at the Medical Research Council Cognition
Brain and Sciences Unit, Cambridge, UK. High-resolution structural MRI
images were acquired using a 3D rapid acquisition gradient echo
sequence with preparation pulses for T1 weighted contrast. The param-
eters of imaging were: TR/TE = 2250/2.99 ms, inversion time = 900 ms,
flip angle = 9°, field of view (FOV) = 256 × 240 × 192 mm³, resolution =
1 mm isotropic, and acquisition time = approximately 4.5 min.
Diffusion-weighted images were acquired using a spin-echo sequence
with two refocusing pulses to minimize distortion induced by eddy cur-
tent. The acquisition scheme entailed 30 diffusion gradient directions for
each of two diffusion sensitivity values (b-value) of 1000 and 2000 s/
mm², and three images with the b-value of 0. The parameters of imaging
were: TR/TE = 9100/104 ms, FOV = 192 mm × 192 mm, voxel size = 2
mm isotropic, 66 axial slices, number of averages = 1, and acquisition
time = approximately 10 min.

2.4. Volume-based morphometric analysis

Cortical regions were segmented on T1-weighted images by a
computational anatomy toolbox CAT12 (http://www.neuro.uni-jen.
debut, based on a review evaluating 20
functional MRI tasks (Duncan, 2006; Duncan and Owen, 2000). Peak
activities from these fMRI studies were smoothed and summed, and the
resulting summed MD map was thresholded to visualize the regions that
were most frequently activated. Coordinates have been transformed into
MNI space, and based on which Duncan listed the coordinates of the MD
map. The coordinates fell into the following fronto-parietal regions: the
inferior frontal sulcus, anterior insula and adjacent frontal operculum,
the pre-supplementary motor area and adjacent dorsal anterior cingulate,
the intraparietal sulcus and adjacent areas (Duncan, 2010). The targeted
two pairs of tracts in the MD system had been reconstructed in a DSI
template (NTU-DSI-122) (Chen et al., 2015; Hsu et al., 2015) in which the
ROIs from the automated anatomical labeling (AAL) system were selected
to reconstruct the targeted tracts (Tzourio-Mazoyer et al., 2002). Having
obtained the summed and smoothed MD maps defined by Duncan and
the ROIs from the AAL atlas for the targeted tracts, we overlapped these
cortical ROIs with the cortical ROIs in the LONI LPBA40 atlas. This was
achieved readily because the coordinates of all ROIs were in MNI space.
Consequently, we identified five pairs of ROIs in the LONI LPBA40 atlas
which were overlapped by both Duncan’s MD maps and the ROIs of the
targeted tracts, and calculated cortical volumes and thickness of these
ROIs. These regions included the superior frontal gyrus (SupFG), the
precuneus (PCu), the inferior frontal gyrus (InfFG), the middle occip-
tal gyrus (MidOccG), and the cingulate gyrus (CingG).

2.5. Diffusion index calculation using regularized mean apparent
propagator MRI

We used regularized mean apparent propagator (ReMAP) MRI to
reconstruct the diffusion propagator from the diffusion MRI signal (Hsu
and Tseng, 2018; Ozarslan et al., 2013). ReMAP MRI fitted the diffusion
MRI signal with the linear combination of Hermite functions, so that the
diffusion propagator can be represented by a few coefficients, serving as
an efficient dimension reduction method. The coefficients of the dif-
fusion propagator, orientation distribution function (ODF) and diffusion
tensor were determined, from which various diffusion indices could be
calculated (Avram et al., 2016). In this study, we calculated axial diffu-
sivity (Da), radial diffusivity (Dr), mean diffusivity (Dm), and generalized
fractional anisotropy (GFA) to represent the microstructural integrity of

| Table 1 | Demographics of the 603 healthy adults in the Cam-CAN cohort. |
|---------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Age (years) Range | 18–30 | 31–40 | 41–50 | 51–60 | 61–70 | 71–80 | 81–90 |
| Subject number | 70 | 97 | 96 | 94 | 100 | 106 | 40 |
| Sex M/F | 30/40 | 53/44 | 43/53 | 51/43 | 54/46 | 48/58 | 22/18 |
| MMSE (Mini-Mental State Examination) range | 25–30 | 25–30 | 26–30 | 26–30 | 25–30 | 25–30 | 25–30 |
| mean (±SD) | 29.12(±1.15) | 29.14(±1.31) | 29.10(±1.15) | 29.21(±0.98) | 28.72(±1.34) | 28.12(±1.54) | 28.00(±1.50) |
| Gf Scores (Scale 2, Form A of Cattell Culture Fair Test) range | 26–44 | 22–44 | 24–43 | 24–43 | 19–41 | 12–42 | 13–36 |
| Mean (±SD) | 37.36(±3.80) | 36.61(±4.59) | 34.80(±4.13) | 32.43(±5.08) | 29.78(±5.93) | 25.86(±5.60) | 22.30(±4.72) |

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WM tracts. The values of $D_A$, $D_R$ and $D_M$ represented, respectively, the first eigenvalue, the mean of the second and third eigenvalues, and the mean of the first, second and third eigenvalues of the diffusion tensor (Basser et al., 2000). The GFA value was defined as the standard deviation of the ODFs in all radial directions divided by the norm of the ODFs (Tuch, 2004).

2.6. Quality assurance of diffusion-weighted images

All diffusion datasets underwent quality assurance procedures, including examinations of the signal-to-noise ratio (SNR), the degree of alignment between T1-weighted images and the diffusion indices’ map including $D_A$, $D_R$, $D_M$ and GFA, and detection of abrupt head motion. SNR was evaluated by calculating the mean signal of an object divided by the standard deviation of the background noise (Dietrich et al., 2007). In practice, the signal was determined using a central square of an image for each slice, and the noise was averaged from four corner regions. Diffusion datasets higher than mean SNR minus 2.5 standard deviations of all participants were included in the study. The degree of within-subject alignment between T1-weighted images and the GFA map was evaluated by calculating the spatial correlation between the WM tissue probability map derived from T1-weighted images and the GFA map. The datasets higher than mean spatial correlation minus 2.5 standard deviations were included in the study. Abrupt head motion or other visible artifacts were manually inspected and removed. After all image quality assurance procedures, the remaining rate was 96.9% (616 out of 636 remained).

2.7. Tract-based analysis for diffusion images

We used an automatic tract-based analysis method, named tract-based automatic analysis (TBAA), to sample the diffusion index values along the tracts in the MD system. The procedures of TBAA have been described previously (Chen et al., 2015). The GFA map was used to register DW images of all the study participants to a standard template space (Anatomical Template and NTU-DSI-122 Diffusion Template) in which 76 major white matter tracts had been built (Chen et al., 2015). Once the registration was completed, position coordinates of the pre-defined tracts were transformed from template space to native space of each individual subject. The values of a diffusion index were sampled on the tract coordinates for each tract. The output of the pipeline was an array of diffusion index values, named connectogram, presenting a total of 76 rows of diffusion index values, 100 values per row, for each subject.

In this study, we focused on the tract integrity of five pairs of WM tracts that physically connected the brain regions in the MD system (Fig. 2). These tracts included bilateral superior longitudinal fasciculi (SLF) divisions 1, 2, and 3 (SLFI, SLFII, and SLFIII), bilateral frontal aslant tracts (FATs), and bilateral superior cingulum bundles (SCBs). In addition to calculating the mean diffusion index values of each tract, we computed the mean values of all tracts in the MD system and the mean values of the networks in the left and right hemispheres. Fig. 2 displayed the list and visualization of the MD regions and the connecting tracts.

2.8. Statistical analysis

Pearson correlation analysis was performed to test the linear relationship between age and Gf scores, as well as between age and structural metrics of the MD system. Partial correlation, controlling for age and sex effects, was performed to estimate Gf associations with cortical volumes and thickness of gray matter and with diffusion indices of WM tracts. Specifically, partial correlation analysis was performed to investigate the associations of Gf scores with the mean $D_A$, $D_R$, $D_M$ and GFA of all tracts in the MD system, mean $D_A$, $D_R$, $D_M$, and GFA of left and right hemispheric tracts, and mean $D_A$, $D_R$, $D_M$, and GFA of each tract. The same analysis was performed to assess the associations of Gf scores with the mean cortical volumes of all MD regions, mean volumes of the left and right MD regions, and mean volumes of each brain region. The associations of Gf with cortical thickness were also analyzed in the same manner. Bonferroni correction was applied to correct for multiple comparisons in partial correlation analyses. Different $P$ value thresholds were employed according to different numbers of comparisons in each level of the MD system.

To investigate whether there was functional lateralization of the left and right MD regions, partial correlations between left and right MD regions were compared using Fisher’s exact test.

3. Results

Significant linear correlations were found between age and Gf $(r = -0.673, p = 0.00)$, cortical volumes $(r = -0.679, p = 0.00)$, cortical thickness $(r = -0.691, p = 0.00)$, $D_A$ $(r = 0.497, p = 0.00)$, $D_R$ $(r = 0.616, p = 0.00)$, $D_M$ $(r = 0.612, p = 0.00)$, and GFA $(r = -0.472, p = 0.00)$ (Fig. 3).
Table 2 lists the partial correlations between Gf and structural metrics of the MD system, i.e. cortical volumes, cortical thickness, and tract integrity (DA, DR, DM and GFA), with age and sex being controlled. We found that both cortical volumes and tract integrity remained significantly correlated with Gf.

Cortical volumes showed significant partial correlations with Gf scores across all levels of the MD system (whole MD system: partial correlation coefficient(r) = 0.218, left MD system: r = 0.218, right MD system: r = 0.215, each region of the MD system: r ranged from 0.152 to 0.199). By contrast, no significant association was found between Gf and cortical thickness (whole MD system: r = 0.073, left MD system: r = 0.077, right MD system: r = 0.066, each region of the MD system: r ranged from 0.008 to 0.094).

For the DA index, significant partial correlations were found in the whole MD system (r = -0.111), left MD system (r = -0.099), and right MD system (r = -0.110). Among the WM tracts connecting the MD regions, significant partial correlations were found in the left FAT (r = -0.131) and right FAT (r = -0.140). The remaining tracts showed no significant associations with Gf after multiple comparison corrections (r ranged from -0.004 to -0.086).

For the DR index, significant partial correlations were found in the whole MD system (r = -0.144), left MD system (r = -0.129), and right MD system (r = -0.151). Among the WM tracts connecting the MD regions, significant correlations were found in the left SLF I (r = -0.146), right SLF I (r = -0.138), right SLF II (r = -0.135), right SLF III (r = -0.117) and right FAT (r = -0.149). The remaining tracts showed no significant associations with Gf after multiple comparison correction (r ranged from -0.031 to -0.146).

For the DM index, significant partial correlations were found in the whole MD system (r = -0.144), left MD system (r = -0.132), and right MD system (r = -0.150). Among the WM tracts connecting the MD regions, significant correlations were found in the left SLF I (r = -0.146) and the right SLF I (r = -0.120), right SLF II (r = -0.137), right SLF III (r = -0.124), left FAT (r = -0.131), and right FAT (r = -0.160). The remaining tracts showed no significant associations with Gf after multiple comparison correction (r ranged from -0.060 to -0.111).

For the GFA index, significant partial correlations were found in the whole MD system (r = 0.130), left MD system (r = 0.126), and right MD system (r = 0.120). Among the WM tracts connecting the MD regions, significant correlations were found in the left SLF I (r = 0.141) and the right SLF I (r = 0.130). The remaining tracts showed no significant associations with Gf after multiple comparison correction (r ranged from 0.021 to 0.141).

Fig. 4 illustrates the results of partial correlation analyses between Gf scores and cortical volumes and the mean DA index values of the left and right MD systems. It is evident that the correlation between Gf and structural metrics was not driven by age (See legends of Fig. 4). Moreover, from Table 2 and Fig. 4, the associations of Gf with cortical volumes or DM did not show obvious differences between the left and right MD systems.

To investigate whether there was the effect of functional lateralization on the left and right MD regions, we applied Fisher’s exact test to compare the difference between left and right MD systems in the partial correlations. Table 3 displays the results of Fisher’s exact test on cortical volumes and WM integrity of DA, DR, DM and GFA. No significant difference was found between left and right MD systems in the partial correlation coefficients.

4. Discussion

In this study, we found significant associations between Gf and both cortical volumes and tract integrity of the MD system across the adult lifespan in a population-based cohort. The linear relationship between cortical volumes and Gf was evident across all levels of the MD system even after controlling for age and sex. For the WM integrity, diffusion indices including DA, DR, DM and GFA displayed linear relationships with Gf scores at various levels of the MD system. Among the diffusion indices, mean diffusivity (DM) had the largest number of tracts showing significant correlations with Gf. Among the 10 WM tracts connecting the MD regions, bilateral SLF I and bilateral FAT exhibited the strongest and significant associations. However, our results did not show significant interhemispheric differences in the associations between structural metrics of the MD system and Gf.

4.1. Frontal-parietal aging model

Based on the network-based perspective of cognitive aging (Greenwood, 2000), we further extended the frontal lobe aging hypothesis to
Fig. 3. Pearson correlations ($r$) between age and the Gf scores, structural metrics of the MD system. Significant correlations were found between age and the Gf scores, cortical volumes (Volume), cortical thickness and tract integrity ($D_A$, $D_R$, $D_M$, and GFA). $D_A$ = axial diffusivity; $D_R$ = radial diffusivity; $D_M$ = mean diffusivity; GFA = generalized fractional anisotropy.
the frontal-parietal aging model for Gf aging. The frontal-parietal aging model was supported by many studies, showing that senescence of complex cognitive functions was attributed to the deterioration of the frontal-parietal circuit (Fjell et al., 2009a; Jung and Haier, 2007; Kennedy and Raz, 2009). Our results support the frontal-parietal engagement of Gf and further clarify that the age-related decline of Gf is consistent with the frontal-parietal model of brain aging, as demonstrated by the Gf-MD relationships.

A previous meta-analysis (Basten et al., 2015) reported that even though the functional and structural clusters of Gf were located in the frontal-parietal circuit, they did not overlap each other. However, in the current study, we found that cortical volumes and WM tracts are integral parts of the MD system, and they support the functioning of Gf. Fedor-enko et al. (2013) argued that the human brain possesses specific regions within the frontal and parietal lobes that are domain- and process-general, hence called MD regions, and such MD brain regions displayed cognitive flexibility responsible for reasoning and solving novel complex problems. In this study, we further demonstrate that Gf is constantly correlated with the MD network from young adulthood up to late life, suggesting that the MD system supports the working of Gf across the adult lifespan.

4.2. White matter tracts connecting frontal and parietal lobes

The WM tracts connecting MD network as a whole showed significant positive partial correlation with the Gf scores. Among these tracts, the functional of SLF I may be critical for Gf. We found that among the five pairs of WM tracts connecting the MD system, bilateral SLF I, which connect the superior frontal gyrus and precuneus, displayed significant positive partial correlations with the Gf scores. This finding highlights the functional significance of SLF I; it may serve as the structural underpinning of Gf. This notion is corroborated by lesion studies (Barbey et al., 2012; Glascher et al., 2009), which have reported that impairments in Gf are associated with the damage to the SLF. SLF I is the only fiber tract connecting the frontal and parietal lobes. Very few studies have discussed SLF I, SLF II and SLF III individually because of their complex pathways. SLF II is the fiber bundle immediately above the arcuate fasciculus, which is located within the superior temporal gyrus. SLF III intersects with other tract bundles such as the AF and corpus callosum (Makris et al., 2005). It follows that SLF I, SLF II and SLF III are difficult to be identified based on an individual’s diffusion MRI data. In the NTU-DSI-122 template, which is the average of the registered DSI data from 122 healthy subjects (Hsu et al., 2015), SLF I, SLF II and SLF III can be reliably segmented because of the high SNR and superior angular resolution of DSI data. It enables diffusion indices of SLF I, SLF II and SLF III to be sampled based on each individual’s DTI data with the aid of the template-based approach employed in this study (Chen et al., 2015).

Our finding also demonstrated the contribution of the FAT. The FAT is a newly identified tract bundle connecting the inferior frontal gyrus (IFG) and the supplementary motor areas (SMA) (Catani et al., 2012; Ford et al., 2010). This short frontal lobe tract bundle connects the Broca’s area and the medial frontal cortex (Ford et al., 2010). In addition to processing language, the functions of FAT also involved executive functions and working memory (Catani et al., 2012).

In this study, we identified two sets of gray-and-white matter structures as the core components of the MD system. The two sets included bilateral superior frontal gyri (SFG), precuneus and the connecting WM tracts of bilateral SLF I, and bilateral IFG, SMA and the connecting WM tracts of bilateral FAT. These gray matter and WM structures simultaneously displayed significant positive correlations with Gf in a large lifespan cohort. The correlations suggest that these core components may play a key role in the functioning of Gf in the entire life. Our findings demonstrate a clear association between Gf-related cognitive functions and brain network, which might serve as a neurological basis for network-based cognitive training and therapeutic interventions.
Generally speaking, microstructural alterations in axons are associated with Dr. For DM, it represents overall mobility of water molecules in the axonal microstructure, and DM increases with the chronic stage of the disease. Many studies have reported that the changes in diffusion indices cannot precisely reflect the microstructural features, and its variation reflects the relative changes in Dx and Dy. For Dz, it represents overall mobility of water molecules in the microstructure, and Dz increases with the chronic stage of fiber degeneration. The diffusion indices change in response to microstructural alterations and these indices are partially interdependent.

Our study explored the relationships between WM tract integrity and fluid intelligence by considering the complete set of the diffusion indices. We found that the values of Dx, Dy and Dz increased, and those of GFA values decreased with age. As compared with Dx, Dy and Dz, all had more tracts showing linear relationships with Gf. The findings suggest that variations of myelin sheath as reflected by Dz and Dm might be the main structural correlates of Gf independent of age.

### 4.4. Functional lateralization of fluid intelligence

Functional lateralization of certain cognitive functions in the human brain has been reported by clinical studies and has long been considered to be beneficial for efficient functioning, particularly right-hemisphere lateralization for visuospatial and attentional processing (Gazzaniga, 1995; Gots et al., 2013; Heilman and Van Den Abell, 1980). Barbe et al. (2014) applied subsets of the Wechsler Adult Intelligence Scale to test the Gf scores of more than one hundred patients with focal brain injuries. They also acquired task functional MRI and diffusion MRI data from the patients to investigate neural substrates of Gf. Using the voxel-based lesion-symptom mapping approach, they found a significant association between the impairment of Gf and the damage to the left Sf (Barbe et al., 2012; Glauch et al., 2010). They found that Gf depended more on the left lateralized network of the frontal and parietal brain regions. It may be due to the involvement of verbal-related ability tested by the
intelligence tests they applied. However, our study applied Cattell Culture Fair test, testing Gf abilities such as pattern recognition, abstract reasoning, and problem solving. There was no verbal-related measurement. Our study found that both cortical volumes and tract integrity within the MD system showed comparable strengths of associations with Gf in the left and right hemispheres. Furthermore, Fisher’s exact test showed no significant difference in partial correlations between left and right MD systems. If hemi-aging asymmetry existed, the right hemispheric structures would have shown stronger associations with Gf which is functionally dominant in the right hemisphere. However, our results indicate that the MD system in the right hemisphere does not seem to be coupled with Gf more tightly than that in the left hemisphere. Therefore, our data of Gf-MD correlations did not support the hemi-aging hypothesis.

These are mixed findings from behavioral and imaging studies in various cognitive domains (Bellis et al., 2000; Goldstein and Shelly, 1981; Heilman and Van Den Abell, 1980; Meudell and Greenhalgh, 1987; Patria et al., 1999; Reuter-Lorenz et al., 2000; Tulving et al., 1994). One possible explanation for the inconsistent results is methodological differences (Dolcos et al., 2002). For example, studies reporting left-lateralized asymmetry used more complex tasks than those reporting no asymmetry (Gerhardtstein et al., 1998). Another possible explanation of the inconsistency might be due to the fact that different brain regions may exhibit different rates of degeneration in different lifespan periods. The inconsistency reflects heterogeneous region-task relationships throughout lifespan.

### 4.5. Negative results of cortical thickness and superior cingulum bundle

In our study, we did not find significant linear relationships between Gf and the cortical thickness within the MD system. Previous studies have reported significant associations of the cortical thickness with general intelligence tests, and the associated regions were located around the prefrontal cortex and temporal lobe (Brouwer et al., 2014; Karama et al., 2011; Menary et al., 2013; Narr et al., 2007). Their findings and our null results of cortical thickness suggest that the cortical thickness might be involved in general intelligence or verbal intelligence, but not in Gf. The underlying mechanism of this disparity requires further investigation.

We did not find significant linear relationships between Gf and the SCB. Recent two studies tested Gf-WM associations with respect to a mediator effect of processing speed. The studies by Haasz et al. (2013) and Kievit et al. (2016) examined the whole brain WM tracts with different research hypotheses for Gf, and the SCB was not among the tracts with significant associations. The null results in the Gf associative studies and ours imply that the SCB might not be a key player in Gf.

### 4.6. Future direction to investigate the lesion brain across adulthood

Although the current study focused on the MD system, we also found significant correlations between Gf and non-MD regions across cortical gray matter and white matter tracts. Previous studies examined the linear relationship between Gf scores and cortical volumes in patients with focal cortical lesions. They found that Gf deficits corresponded to the damage confined to the frontal and parietal cortices, and supported the engagement of a network-wise framework of Gf function (Barbey et al., 2014; Glashcer et al., 2009; Woolgar et al., 2010). Based on such findings, this study investigated the Gf-MD correlations across a normal adult cohort and provided evidence to support this hypothesis. At the same time, the Gf-non-MD correlations suggest that the MD system was not the only neural substrate responsible for Gf in non-lesion brain. It requires further works to clarify the difference in Gf-brain relations between lesion brain and non-lesion brain.

### 4.7. Limitations

The current study has limitations. First, our study was a cross-sectional study instead of longitudinal cohort study. The longitudinal research design following participants’ changes with age can better reflect the lifespan patterns of human brain and behavior. However, it is very difficult to track a life-long longitudinal cohort. The cross-sectional estimates from a sufficiently large population, similar to that used in this study, may indirectly reflect within-person changes over time. Second, the cohort did not include the developmental stages across the childhood and adolescent periods; instead, the study focused on the 18–88-years age group. Therefore, the present study could not provide an overall lifespan perspective of the relationship between Gf and the MD system. Third, we included four domains of Gf but they were all subtests of a single test. The present finding for the association between Gf and the MD system may only represent a restricted perspective of human Gf (Kievit et al., 2016).
5. Conclusion

By examining a large adult population across a wide age range using the same MRI scanner, we confirmed the association of Gf with the MD system in the context of aging. We found that the association remained significant in the entire adult lifespan despite simultaneous decline of Gf and the MD system. Our results suggest that the MD system might be the biological underpinning of Gf. Because the MD system is composed of gray matter and WM structures in the fronto-parietal regions, our findings support the fronto-parietal model of cognitive aging. However, we did not find interhemispheric differences in the Gf-MD correlations, not supporting the hemi-aging hypothesis. We further identified the core components within the MD system that showed unified associations with Gf, which included bilateral SFG, precuneus and the connecting tracts of SLF I, and bilateral IPL, SMA and the connecting tracts of FAT. A longitudinal study or local intervention study should be conducted to verify the causal relationships between Gf and core MD components.

CRediT authorship contribution statement

Pin-Yu Chen: Conceptualization, Writing - original draft, Visualization. Chang-Le Chen: Formal analysis, Visualization. Yung-Chin Hsu: Software. Wen-Yih I. Tseng: Resources.

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There is no financial interest or relationship to disclose with regards to the subject matter of this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2020.116576.

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