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Evidence for the Independent Review of SFC's Research Pooling Initiative

I am involved in SFC's Research Pooling Initiative through long-term research collaboration with the members in **SINAPSE** (**S**cottish **I**maging **N**etwork: **A** **P**latform for **S**cientific **E**xcellence). The collaboration started from a workshop entitled "RSE/MOST Workshop on Brain Neuroscience" held from November 2nd – 5th, 2015, Tainan, Taiwan. The meeting was intended to seek opportunities of bilateral collaboration between neuroscientists in Royal Society of Edinburgh (RSE) and Taiwanese counterpart. In that workshop, I met Prof. David Wyper, then CEO of SINAPSE, and Dr. Kristin Flegal, SINAPSE lead scientist. We agreed to leverage the strengths on both sides to unravel the mystery of brain ageing using advanced neuroimaging technologies. After 6 months of preparation, SINASE sent Dr. David Dickie at University of Edinburgh and Dr. Gordon Waiter University of Aberdeen to visit my lab from May 20th to 26th, 2016. After a week-long meetings and discussions, we decided to study the ageing change of white matter tracts by analyzing 9000 more diffusion MRI datasets in UK Biobank. Specifically, we planned to use a novel technique "tract-based automatic analysis" to analyze tract integrity of 76 tract bundles of the brain. In the following year, we obtained the permission from UK Biobank which allowed us to conduct our project using the UK Biobank datasets, and allocated the high performance computing resource at University of Aberdeen for image processing. We also held several conference calls to discuss the contents and structures of the UK Biobank data. To launch the cooperative tasks, I, Dr. Eric Hsu (then my post doc) and Yao-Chia Shih (then my PhD student) visited University of Aberdeen from September 16th to 22nd, 2017. During that week, we set up the algorithm and had it run on high performance computing facilities at University of Aberdeen. We set up the workflow of analysis including quality assurance procedures, execution of automated algorithm, statistical analysis of output data, and interpretation of the results, and also the time schedule of data analysis, progress review, and manuscript writing. In 2018 May, we completed tract-specific analysis over approximately 9000 diffusion tensor imaging datasets from UK Biobank,

and built age-specific templates and produced age trajectories of white matter tracts across adult life span. To review the results and discuss the plan for manuscript preparation, Dr. Gordon visited our lab from May 7th to 10th, 2018. In December, we finished the whole analysis and submitted an abstract to the annual meeting of Organization of Human Brain Mapping 2019 (See Appendix). Now, the manuscript is under preparation for submission to a prestigious journal in neuroscience.

The funding of the exchange visit was provided by Royal Society of Edinburgh and Taiwan Ministry of Science and Technology under the International Exchange Programme - Bilateral. Through the collaboration, we got to know many researchers in Scotland and appreciated the high quality research works of theirs. We also admired the vision of Scottish government willing to make long term commitment to advance the frontiers of neuroscience and undaunted courage to establish data haven that will benefit many generations of society.

Appendix

Microstructural changes of white matter tracts across late lifespan on 7,167 UK Biobank Participants

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Introduction:

Characterizing age-related changes in white matter microstructure is crucial to understanding the biological processes of brain ageing. Cox et al. reported age-related changes of white matter tracts in 3,513 healthy people aged 44 to 77 years from the UK Biobank [1]. The present study extended the previous study using automatic tract-based analysis of 76 tracts in 7,167 healthy participants aged 47 to 76 years. We examined the major hypotheses in the field of ageing research by identifying the characteristics of age-related changes in white matter tracts.

Methods: We retrieved magnetic resonance imaging (MRI) data from 7,167 generally healthy participants (mean age 62.3±7.25 years, range 47–76 years, male: 3,368 males) in the UK Biobank. **MRI data acquisition:** MRI scanning was performed on a 3T Siemens Skyra System, with a 32-channel RF receive head coil. T1-weighted images were acquired using a 3D magnetization-prepared rapid gradient-echo pulse sequence: TR/TE = 880/2000 ms, FOV = 208 x 256 x 256 mm^3, and resolution= 1 x 1 x 1 mm^3. Diffusion MRI utilized a spin-echo echo-planar imaging sequence with 10 baseline images (b = 0 s mm^{-2}), 50 diffusion-weighted images with b = 1,000 s mm^{-2} and 50 images with b = 2,000 s mm^{-2}; imaging parameters: FOV = 104 x 104 mm, matrix size = 52 x 52, and slice thickness = 2 mm. **Data Analyses:** Diffusion-weighted images were processed to generate 4 diffusion indices including generalized fractional anisotropy (GFA), axial diffusivity (AD), mean diffusivity (MD), and radial diffusivity (RD). We used whole brain tract-based automatic analysis to obtain diffusion index profiles of 76 white matter tract bundles. We also sampled the tissue probability map along each tract to correct the partial volume effects of cerebrospinal fluid. Data analysis was conducted using high performance computing facilities at the University of Aberdeen. Linear regression analysis was performed for each tract to determine the slope of change in each diffusion index with age. We divided the slopes into four rates of change based on the histogram of the slopes.

Results: Table 1 lists the slopes of tract integrity change with age in three fiber systems and 10

subsystems. The tract integrity displayed differential age-related changes; the rate of change was highest in the association fibers, followed by the commissure fibers, and lowest in the projection fibers. Among the 10 subsystems, the corticospinal tracts did not exhibit age-related change. In the other 9 subsystems showing significant ageing effect, only the anterior and posterior commissure fibers showed increased integrity with age. Figure 1 shows color-coded slopes of GFA in 76 individual tracts. The fibers showing fastest decline included the right uncinate fasciculus, right superior longitudinal fasciculus, bilateral inferior fronto-occipital fasciculi, bilateral fornices and stria terminalis, the callosal fibers connecting bilateral prefrontal lobes and hippocampi. Notably, the anterior commissure showed increased integrity with age, and the corticospinal tracts were least affected by ageing.

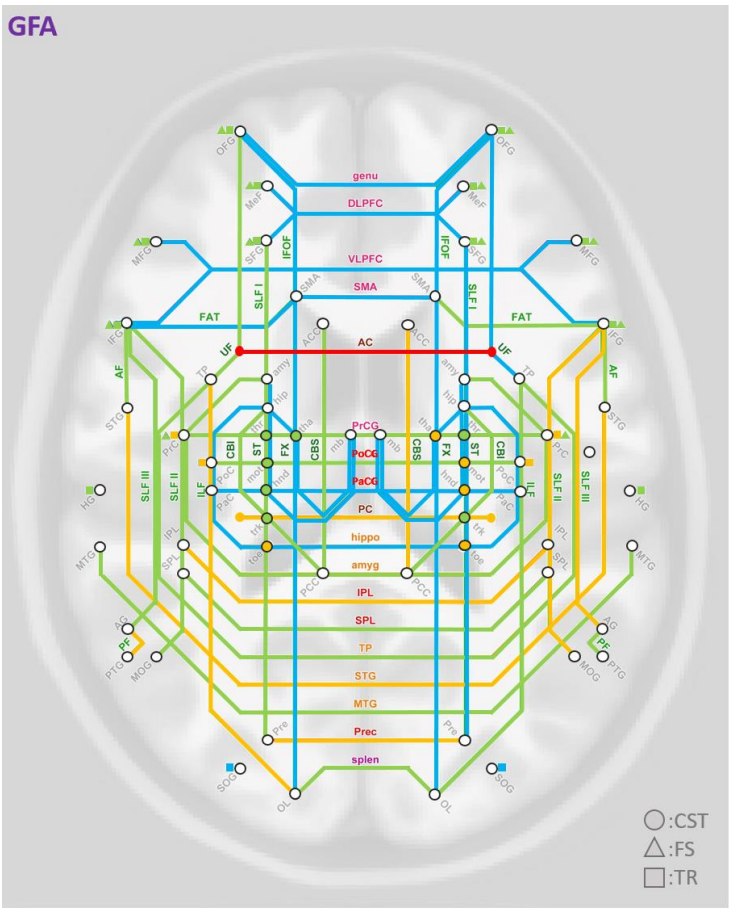
Discussion: We have identified three major changes in tract integrity during normal ageing. First, most of the tracts connecting the prefrontal lobes show dramatic decline with age. These findings are consistent with the frontal lobe hypothesis, which states that dramatic ageing decline of neural tissue in the prefrontal cortex causes rapid decline of cognitive functions supported by the affected areas [2-4]. Second, the apparent decline of the fibers in the limbic system and callosal fibers connecting bilateral hippocampi provide the structural basis of the memory decline during ageing [5,6]. Third, the minimal ageing effects on the corticospinal tracts and a reverse ageing effect on the anterior commissure are counter-intuitive and warrant further study to clarify the mechanisms involved.

Table 1: The rate of change in diffusion indices with age in three fiber systems and 10 subsystems

Systems	Subsystems	GFA (p-value)	AD (p-value)	MD (p-value)	RD (p-value)
Association		-0.00028 (0.00†)	0.00203 (0.00†)	0.00182 (0.00†)	0.00171 (0.00†)
Projection		-0.00015 (0.00†)	0.00102 (0.00†)	0.00073 (0.00†)	0.00058 (0.00†)
Commissure		-0.00022 (0.00†)	0.00268 (0.00†)	0.00213 (0.00†)	0.00186 (0.00†)
Association	Limbic System	-0.00038 (0.00*)	0.00344 (0.00*)	0.00330 (0.00*)	0.00323 (0.00*)
	Cortical-cortical	-0.00021 (0.00*)	0.00114 (0.00*)	0.00089 (0.00*)	0.00076 (0.00*)
Projection	Corticospinal Tract	-5.42e-06 (0.8238)	0.00041 (0.00*)	0.00026 (0.00*)	0.00019 (0.00*)
	Frontal-Striatum	-0.00032 (0.00*)	0.00161 (0.00*)	0.00121 (0.00*)	0.00101 (0.00*)
	Thalamic Radiation	-0.00017 (0.00*)	0.00124 (0.00*)	0.00087 (0.00*)	0.00069 (0.00*)
Commissure	Commissure	0.00076 (0.00*)	0.00305 (0.00*)	0.00158 (0.00*)	0.00084 (0.00*)
	Frontal	-0.00069 (0.00*)	0.00154 (0.00*)	0.00156 (0.00*)	0.00158 (0.00*)
	Parietal	-0.00014 (0.00*)	0.00226 (0.00*)	0.00166 (0.00*)	0.00136 (0.00*)
	Temporal	-0.00020 (0.00*)	0.00439 (0.00*)	0.00363 (0.00*)	0.00325 (0.00*)
	Occipital	-0.00027 (0.00*)	0.00116 (0.00*)	0.00096 (0.00*)	0.00085 (0.00*)

Note. Significant difference after Bonferroni correction(†P<0.0167, *P<0.005)

Figure 1: Diagram of 76 tracts color-coded with slopes of GFA



marked decrease slope< -0.5×10^{-3}

slight decrease -0.5×10^{-3}< slope < 0

slight increase 0 < slope < 0.5×10^{-3}

marked increased 0.5×10^{-3} < slope

Tract names

AF (arcuate fasciculus)
CBS (superior cingulum bundle)
CBI (inferior cingulum bundle)
FAT (frontal aslant tract)
FX (fornix)
IFOF (inferior fronto-occipital fasciculus)
ILF (inferior longitudinal fasciculus)
PF (perpendicular fasciculus)
SLF (superior longitudinal fasciculus)
ST (stria terminalis)
UF (uncinate fasciculus)
Hnd (CST of hand)
Trk (CST of trunk)
Mot (CST of mouth)
Toe (CST of toe)
Thr (CST of trunk)
AC (Anterior commissure)
PC (Posterior commissure)
Genu (corpus callosum of genu)
Splen (splenium)

Brain regions

OFC (orbitofrontal cortex)
IFG (inferior frontal gyrus)
MFG (middle frontal gyrus)
SFG (superior frontal gyrus)
MFG (medial frontal gyrus)
HG (Heschl's gyrus)
SOG (superior occipital gyrus)
VLPFC (Ventrolateral prefrontal cortex)
DLPFC (Dorsolateral prefrontal cortex)
SMA (supplementary motor areas)
PrCG (precentral gyrus)
PaCG (paracentral gyrus)
IPL (inferior parietal lobule)
PoCG (postcentral gyrus)
SPL (superior parietal lobule)
STG (superior temporal gyrus)
MTG (middle temporal gyrus)
TP (temporal pole)
Hippo (hippocampus)
Amyg (amygdala)
Prec (precuneus)

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