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## Flight training and the anterior cingulate cortex

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Pilots are considered the final line of defense for aviation safety. Before becoming a pilot, an ab initio pilot must undergo systematic flight training. This study included 25 male flying cadets. Kendall's coefficient of concordance was used to measure the regional homogeneity of the time series of a given voxel with its 26 nearest neighboring voxels. This operation was performed for all voxels to generate a regional homogeneity map for each participant based on Kendall's coefficient of concordance. A partial correlation analysis was performed to examine the relationship between regional homogeneity maps and flight training hours. We found that the anterior cingulate cortex in the ab initio group was significantly positively correlated with flight hours. These results suggest a potential relationship between flight training experience and the functional properties of the anterior cingulate cortex.

Keywords Ab initio, Brain mechanism, Functional MRI, Regional homogeneity

Civil aviation safety in Asia has continuously improved in recent years. This is the joint result of several efforts. Pilots are considered the final line of defense for aviation safety. The pilot must manage the flight path of the aircraft, monitor current and projected trajectories, and monitor the aircraft status. Moreover, the pilot should always be prepared for emergencies. During flight, pilots must constantly scan the flight instruments to determine which control inputs are required. Neurophysiological measures, such as eye-related movements, electroencephalography, and functional MRI (fMRI), have been used in the aviation industry to detect the workload levels and operational errors of pilots<sup>1–3</sup>. FMRI studies on the physiological mechanisms associated with flight have found that pilots exhibit increased functional dynamics<sup>4</sup>. Therefore, being a pilot is a special profession that requires professional training.

Traditional airline flight training is based on previous accidents. Ab initio should fly in a simulator and real aircraft for many hours to learn how to gain situational awareness, maintain the attitude of the aircraft, perform multitasking simultaneously and handle an emergency. In practice, the assessment of flight training largely depends on the evaluations of flight instructors. This assessment is subjective and focuses only on behavioral level. However, the relationship between flight training and brain function has rarely been studied. Electroencephalography and functional near-infrared spectroscopy had been used to measure the neurophysiology of learning. Using a pilot task, researchers found that flight training changed the beta-band network measures over the training course<sup>5</sup>. In another study, frontal theta power decreased over five days of training, while performance increased<sup>6</sup>. The theta-band power generally increased under a high workload and decreased as the pilots became more experienced. Since it always exhibited general decrease over flight training sessions<sup>7</sup>, the frontal theta power can be used as an index of experience or training level. In addition, during flight training, the global efficiency of the functional network of participants in the high-frequency band first decreased and then increased, whereas the local features exhibited opposite patt<sup>5</sup>. These results suggest that brain features can be used as biomarkers to quantify the flight training progress.

FMRI has been widely used to investigate the neural mechanisms of the brain because of its high spatial resolution and safety. Owing to the high cost and relatively small number of pilots, there have been relatively few MRI studies on pilots compared to psychosis and neurosis, especially on flight training. Voxel-based morphometry study found that left ventral premotor cortex, anterior cingulate cortex (ACC) and the supplementary eye field exhibited significant gray matter density increase in glider pilots<sup>8</sup>. There were also increased gray matter volume in the lingual gyrus, inferior frontal gyrus, supramarginal gyrus and postcentral gyrus in airline pilots<sup>9</sup>. FMRI studied found that frontal regions and caudate nucleus in pilots contribute to decision making and aviation track-following task<sup>10,11</sup>. In general, the frontal cortex, the somatosensory and motor cortex and ACC may involve in flying. The frontal lobe plays an important role in cognitive control<sup>12</sup>. ACC involves in conflict monitoring and motor related cognitive control<sup>13,14</sup>. The sensorimotor cortex is associated with the pilot's manipulation of the aircraft's movement and real-time monitoring of the internal and external environment of the aircraft. In our

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previous studies, functional connectivity characteristics and white matter fiber tracts were altered after flight training<sup>15–17</sup>. These results suggest that MRI can be used to further explore the neural mechanisms of flight training.

Operational training induces the functional reorganization of the brain<sup>18</sup>. Meanwhile, training can also benefit from neurophysiology. Therefore, we hypothesized that flight training could be related to some functional properties in the frontal cortex, the somatosensory and motor cortex and ACC, and these brain functional properties might serve as an additional, insightful method for the evaluation and personalization of flight training.

In this study, we attempted to identify the brain regions that are directly related to flight training time by calculating the correlation between the local characteristics of brain function and flight training duration. Kendall's coefficient of concordance (KCC), which represents the similarity between several time series, was used to represent the local characteristics of brain function. This data-driven method can reveal unpredictable alterations in brain function caused by flight training. Studies have shown that regional homogeneity (ReHo) based on KCC can be used to identify the intrinsic brain dynamics of individual experiences<sup>19,20</sup>. In the current study, we used the KCC ReHo as data-driven method to explore areas of the brain that are related to flight training. Our results can provide a better understanding of the neural mechanisms involved in flight training.

#### Methods

#### Study design

This study included 25 flight cadets from the Civil Aviation Flight University of China who were recruited through advertisements. They were all juniors and the actual flight training time ranged from 101.5 to 249 h (including flight simulator and training plane hours). The aircraft types C172R and DA-42 were used. None of the participants had a history of brain injury or neurological or psychiatric illness.

The Ethics Committee of the University of Electronic Science and Technology of China (Chengdu, China) approved the study protocol (No. 2019-042019). All experiments were performed in accordance with the relevant guidelines and regulations. Written informed consent was obtained from all participants after the nature of the study was explained individually.

#### Data acquisition

The flight training time for each cadet was collected from the records of their flight training systems. MRI images were obtained using a 3-T MRI scanner (DISCOVERY MR 750; GE Healthcare, Waukesha, WI, USA). Each subject underwent a T1-weighted anatomical and fMRI. A three-dimensional spoiled gradient-echo pulse sequence was used to collect T1 data. The repetition time (TR) = 5.976 ms, echo time (TE) = 1.976 ms, flip angle = 9°, field of view (FOV) =  $256 \times 256 \times 154$  mm, matrix =  $256 \times 256$ , and slice number = 154. The voxel size = 1 mm × 1 mm × 1 mm. Participants were asked to keep their eyes closed and avoid falling asleep. A gradient-echo echo-planar imaging sequence was used to collect functional data with the following parameters: TR, 2000 ms; TE, 30 ms; flip angle, 90°; FOV, 240 mm × 240 mm × 140 mm; matrix,  $64 \times 64$ ; and slice thickness, 4 mm (no gap). The in-plane voxel size was 3.75 mm × 3.75 mm × 4 mm. Each volume consisted of 35 slices. Finally, 255 volumes were acquired from each participant.

#### MRI data preprocessing

Preprocessing was performed with SPM12 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). The first five volumes of fMRI data were discarded for magnetization equilibrium. The remaining 250 scans were subjected to slice timing and head-motion correction. Participants with excessive head motion (2 mm in any direction or 2°rotation in any direction) were excluded from further data analysis.

The T1 images were segmented into gray matter, white matter, and cerebrospinal fluid. The functional images were then co-registered with the gray matter images. Subsequently, the resulting images were normalized to the standard Montreal Neurological Institute template at a  $3 \times 3 \times 3$  mm<sup>3</sup> resolution. The EPI images were then processed to remove the linear trends and bandpass filtered (0.01–0.08 Hz) to restrict low-frequency drift and high-frequency noise. Finally, multiple linear regression analysis was used to remove the white matter signal, cerebrospinal fluid signal, and head motion parameters (six rigid-body parameters).

#### **ReHo analysis**

We used RESTplus to calculate the ReHo indices<sup>21</sup>. In fMRI, the KCC can be used to measure the similarity of the time series of a given voxel with its nearest neighbors in a voxel-wise manner, which can be referred to as the KCC ReHo<sup>22</sup>. A high level of ReHo suggests that voxels within a functional brain region are temporally homogeneous.

Specifically, the KCC was used to measure the regional homogeneity of the time series of a given voxel with its 26 nearest neighboring voxels. These voxels are neighbors of the vertices of a given voxel. Each voxel has 8 vertices, and every eight voxels share one vertex. After removing the double-counted cubes, 26 neighbors remained. This operation was performed for all the voxels to generate a KCC ReHo map. The map was then normalized to minimize individual variations and spatially smoothed using an isotropic Gaussian kernel (8 mm full width at half-maximum, FWHM).

A partial correlation analysis was performed to examine the relationship between the ReHo maps and flight hours. This analysis was performed voxel-wise. Gaussian Random Field (GRF) correction (p < 0.05) with an initial height threshold of p < 0.001 was performed to correct for multiple comparisons.

|                           | flying cadets<br>(N = 25) |       |
|---------------------------|---------------------------|-------|
|                           | М                         | SD    |
| Age (years)               | 20.84                     | 0.69  |
| Gender (% male)           | 100%                      |       |
| Education (years)         | 14                        |       |
| Handedness (% right)      | 96                        |       |
| Total flight time (hours) | 221.96                    | 30.90 |

 Table 1. Demographic characteristics of the participants M: mean value; SD: standard deviation.

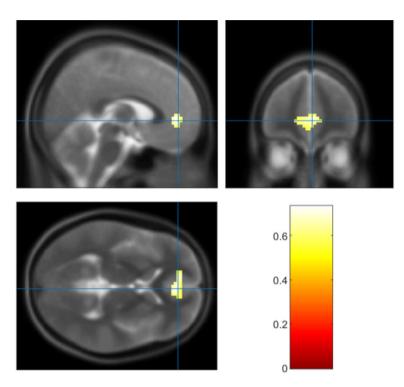


Fig. 1. Brain regions with significant correlation with flight hours (GRF-corrected, p < 0.05; initial height threshold, p < 0.001).

## Results

### Participants

No participants were excluded because of excessive head motion. Twenty-five cadets were included in the study. They were all male and the average age was 20.84 years. The total number of flight hours was 221.96. Demographic parameters are listed in Table 1.

#### Brain-flight experience correlation data

A significant positive correlation between ReHo and flight hours was observed in the ACC (GRF-corrected, p < 0.05; initial height threshold, p < 0.001) (Fig. 1). The peak positive correlation coefficient was 0.73, which means that the longer the flight hours, the higher the local temporal homogeneity in the ACC. In other words, as the flight experience increased, the functional activity in the ACC region became more consistent.

#### Discussion

The present study used the ReHo approach to investigate the relationship between local brain characteristics and flight training. Our results revealed that the ACC of the ab initio group was significantly correlated with flight hours. A previous study also found that the ACC gray matter density in glider pilots increased significantly<sup>8</sup>. These results suggest a potential relationship between flight experience and the functional properties of the ACC.

ACC is located on the anterior medial surface of the brain. However, layer 5 of the ACC contains a distinctive class of large spindle-shaped neurons that are present only in humans and their closest relatives, such as great apes<sup>23,24</sup>. Retrograde tracers have shown that spindle neurons have long-distance projections<sup>25</sup>. In humans, the ACC receives strong projections from the amygdala and has strong interconnections with the ventrolateral prefrontal cortex<sup>26,27</sup>. The basal ganglia also receive dense ACC input<sup>27</sup>. Therefore, there are strong connections

between the ACC and numerous brain regions, and ACC function is more likely to be related to higher mental functioning.

Neurophysiological and imaging evidence suggests that ACC neurons resemble reward prediction errors, reflecting comparisons between expected outcomes and received outcomes<sup>28,29</sup>. Furthermore, the ACC monitors performance and adjusts behavior to optimize payoffs<sup>30,31</sup>. The ACC appears to be important for flexible behavior because it identifies the importance of stimuli in a changing environment<sup>32</sup>. Furthermore, ACC neurons can encode second-order statistical information, such as how uncertain or subjectively valuable a human is regarding the outcomes of resolution, which is crucial for learning<sup>32</sup>.

Because of these functions, the ACC is believed to play an important role in decision making. During decision making, information sampling appears to be more related to ACC neuronal activity than to other prefrontal areas<sup>33</sup>. Functional event-related MRI studies have also identified the importance of the ACC in reward-related decision-making<sup>34,35</sup>. The striatum, amygdala, and orbitofrontal cortex are implicated in processing decision outcomes, whereas the ACC and dorsolateral prefrontal cortex anticipate rewards and make decisions<sup>36</sup>. When encountering new options, humans first seek information to resolve uncertainty; then, they show attentional bias toward the most certain choice based on their evaluations<sup>37,38</sup>. The ACC suppresses interference and obstruction during attentional control<sup>39,40</sup>. Information seeking requires humans to detect uncertain outcomes and mediate action selection relative to predicting the time of uncertainty resolution<sup>41</sup>. Functions such as integration of feedback across multiple timescales and contexts, are crucial in volatile flight contexts.

In addition, the ACC contributes to working memory, which is also important for flight. ACC infarctions can cause persistent working memory dysfunction<sup>42</sup>. Neuroimaging data have also shown that ACC activity is involved in working memory performance. During the reading span test, the fMRI signal of the ACC increased significantly, in addition, higher activation levels are associated with better working memory performance<sup>43,44</sup>.

It has been suggested that the function of the ACC is related to guiding information-seeking and decisions about whether to explore or engage in the same behavior as before. These functions contribute to learning and behavioral changes. In conclusion, the overall function of the ACC is to use outcome-related information to guide action selection through a cost-benefit analysis by integrating information on past outcomes.

The flight environment is volatile. Outcome distributions often change without warning. Pilots often engage with uncertain stimuli. They must choose to obtain rewards and reduce uncertainty about their future choices. During flight, the pilot builds a model of the environment and estimates the risks associated with the options. This information could be used in future studies. During decision-making, pilots must generate hypotheses regarding their choices. The ACC is also involved in these processes<sup>41</sup>.

Participants in this study must complete their theoretical studies in the classroom (mainly cognitive skills) in the first 2 years and complete their flight training (mainly "hand-eye" skills) in the flight simulator (50 h) and training plane (200 h) for the last 2 years. They can then apply for a pilot license. During the experiment, they completed their theoretical studies, and the actual flight training time (including the flight simulator and training plane hours) ranged from 101.5 to 249 h. During flight training, the cadets controlled the aircraft according to its current state. Owing to the complex and changeable flight environment, the cadets had to learn to master the plane and make real-time decisions about the next step based on the current situation with caution, as the consequences of wrong decisions are often very serious. Therefore, the ACC of the ab initio group exhibited a significant correlation with flight training.

The main weakness of this study was its small sample size. The small sample size also resulted in an insufficient variation in flight hours. The current findings should be confirmed by using a larger sample size. Further, this was a correlational study that, could only explain the correlation and could not be used to make a causal inference. Additionally, owing to the rarity of female cadets, there were no female participants in this sample. Therefore, the results of this study cannot be generalized to female pilots.

#### Conclusions

In conclusion, we investigated the relationship between flight training hours and functional brain properties in 25 cadets. The regional homogeneity of the ACC in the ab initio group was significantly positively correlated with flight hours. The ACC is involved in flexible behavior and decision-making. Day-to-day flight training includes real-time decision making in a complex and changing environment. These results suggest a potential relationship between flight training experience and the functional properties of the ACC.

#### Data availability

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: https://pan.baidu.com/s/1C0dLdo4xv9IODWSwXNzAlQ?pwd=9tjz.

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#### Author contributions

X C, H-M W and C L designed the experiment and wrote the article and gave final approval of the version to be published; X-T and M-J D collected and analyzed the data; they also revised the article critically.

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#### Declarations

#### **Competing interests**

The authors declare no competing interests.

#### Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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