

COVID-19 vaccine-hesitancy is associated with lower cortical volume in elderly individuals

Fardin Nabizadeh^{1,2,*}, and the Alzheimer's Disease Neuroimaging Initiative^{**}

- 1- Neuroscience Research Group (NRG), Universal Scientific Education and Research Network (USERN), Tehran, Iran
2- School of medicine, Iran University of Medical Sciences, Tehran, Iran

Abstract

Background: According to a large number of scientific reports, the main problem is COVID-19 vaccine hesitancy which slowed down the vaccination program. Previous studies revealed that COVID-19 vaccine hesitancy is associated with lower cognitive performance. However, the neurobiology of such behavior is less known, and investigating the brain structural patterns in this regard can extend our knowledge on the basis of this behavior. This study aimed to investigate the link between brain structural features including cortical and subcortical volume with COVID-19 vaccine hesitancy in elderly individuals.

Methods: A total of 221 healthy subjects without any cognitive impairment with a mean age of 63.7 ± 6.1 were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Overall, 87 vaccine-hesitant (VH) and 134 vaccine-accepted (VA) were entered into this study. The difference in the volume of cortical and subcortical regions was investigated between VH and VA groups.

Results: There was no significant difference in cognitive status measured by MMSE, MoCA, ADAS-cog, and RAVLT between VA and VH groups ($P > 0.05$). The analysis showed that VA subjects had significantly higher left pars orbitalis ($P: 0.013$), left precentral ($P: 0.042$), right caudal anterior cingulate ($P: 0.044$), and right isthmus cingulate ($P: 0.013$) volume compared to the VH group. There was no significant difference in other cortical and subcortical regions.

Conclusion: In conclusion, this finding demonstrated that in the era of complicated decision-making due to social media reports, elderly adults with smaller frontal and cingulate regions are more likely to be vaccine-hesitant. These findings can highlight the link between cortical regions and health-protective behaviors such as taking up the offer of vaccination.

Keywords: COVID-19, vaccine, hesitancy, cognition, brain, cingulate

*Correspondence to Fardin Nabizadeh, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

Email:
Fardinnabizade1378@gmail.com

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Introduction

Since December 2019, after the deceleration pandemic by World Health Organization (WHO), coronavirus disease 2019 (COVID-19) contributed to tremendous loss of life worldwide (1). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a highly transmissible disease causing acute respiratory disease threatens public safety (2). While early intervention by several governments was successful such as contact tracing, self-distancing, and wearing masks; highly

contagious variants reversed the infection rate and brought the virus out of control (3). However, the scientific community believed that developing wide-scale immunity using effective vaccines can control the pandemic (4). Nowadays, scientists and pharmaceutical companies began to collaborate and produce effective vaccines for SARS-CoV-2 (4). The current strategy for controlling the pandemic is vaccinating the population as much as possible and relying on those who recovered from the disease and are partially immunized (5). However, according to a large number of scientific reports, the

main problem now is COVID-19 vaccine hesitancy which slowed down the vaccination program (6). The “delay in acceptance or refusal of safe vaccines despite availability of vaccine services” is vaccine hesitancy according to the WHO definition (7). Since the first ideation of fighting COVID-19 by vaccines, social media, and public discourse sparked on whether receive the vaccine or not. Then vaccine hesitancy became a crucial issue that influence public health (8). Refusing the getting vaccinated is more worrying, especially in older adults which have higher rates of mortality and experience more severe disease course due to COVID-19 similar to other infections as well (9). As the older adult population is more vulnerable to COVID-19, there is a need for a higher percentage of vaccination in this group (10).

Previous studies revealed that COVID-19 vaccine hesitancy is associated with lower cognitive performance (11, 12). Such a health protection behavior is a complex task including knowledge, decision-making, and planning. The role of cognition in healthy and preventive behavior has been investigated and it was proposed that higher cognitive ability resulted in better management of preventive behaviors and more effective treatment (13). Moreover, individuals with higher cognitive ability are more likely to choose a healthy diet and have less probability of smoking cigarettes based on existing literature (14, 15). Also, in people with an elevated risk of colorectal cancer, subjects with higher scores on cognitive tests participate more in screening programs (16). All this evidence highlights the role of cognitive function in health protection behaviors.

A vast majority of studies have focused on the relation between brain structure and cognitive function to understand the neurobiological basis of cognitive process (17). It is well-established that lower gray and white matter volume reflects lower cognitive ability in healthy individuals (18). However, the role of cortical gray matter such as medial temporal and subcortical regions including the hippocampus seems to be more prominent in cognitive performance (19-21).

Although previous studies investigated the psychological and cognitive ability of people with more intention to health protection behavior such as COVID-19 vaccine acceptance, investigating the brain structural feature can extend our knowledge on the basis of this behavior. This study aimed to investigate the link between brain structural features including cortical and subcortical volume and COVID-19 vaccine hesitancy in healthy elderly individuals.

Materials and methods

Subjects

Data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was established in 2003 as a public-private partnership led by Principal Investigator Michael W. Weiner, MD. The main purpose of ADNI is to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessments can be used to track the development of MCI and early AD. The data of healthy subjects without any cognitive decline were extracted.

Classification

Based on ADNI concurrent medication file which includes all medication records, the participants were asked about their COVID-19 vaccination status. The subjects who did not receive the COVID-19 vaccine are categorized as whom does not accept or delayed the COVID-19 vaccination and are vaccine-hesitant (VH)(n=87). It should be mentioned that all entered subjects had complete follow-up and medication profiles during the COVID-19 pandemic and were asked for COVID-19 vaccination status. Also, all participants had access to the COVID-19 vaccine. The participants who received the COVID-19 vaccine (any dosage) were categorized as vaccine accepted (VA)(n=134). The decision to get vaccinated was made by the patients themselves (active refusal).

Cortical and subcortical volume

MRI scans were processed at the ADNI core laboratory. Cortical reconstruction and volumetric segmentation using the FreeSurfer image analysis suite are freely available for download (surfer.nmr.mgh.harvard.edu). Processing of images includes averaging of volumetric T1 weighted images and motion correction (22), using a procedure to remove non-brain tissue (23), automated Talairach transformation, intensity normalization, tessellation of the boundary between gray matter and white matter, automated topology correlation, and optimally placing the border between gray and white matter and gray matter and CSF. The full procedure is described at (adni.loni.usc.edu). The volume of the following cortical and subcortical regions was extracted and entered into the study synthesis based on the Desikan–Killiany (DK) atlas (24): Caudal middle frontal, frontal pole, lateral orbitofrontal,

Table1. Participants characteristics

| Characteristic | VA (n=134) | VH (n=87) | P value |
|-----------------------------|------------|------------|---------|
| Age, mean (SD), years | 63.5 (5.3) | 64.1 (7.0) | 0.06 |
| Female sex, No. (%) | 83 (61.5) | 57 (65.5) | 0.591 |
| Education, mean (SD), years | 16.5 (2.5) | 16.3 (2.4) | 0.638 |
| Married, No. (%) | 100 (74.6) | 61 (70.1) | 0.462 |

Abbreviations: VA, Vaccine accepted; VH, Vaccine hesitant

Table 2. Participants cognitive status

| Cognitive test | VA (n=134) | VH (n=87) | P value |
|-------------------------------------|-------------|-------------|---------|
| MMSE score, mean (SD) | 28.2 (2.2) | 28.7 (1.8) | 0.348 |
| ADAS-cog 11 item score, mean (SD) | 7.0 (5.8) | 6.0 (4.2) | 0.43 |
| ADAS-cog 13 item score, mean (SD) | 10.7 (7.7) | 9.1 (6.3) | 0.364 |
| RAVLT immediate recall, mean (SD) | 42.9 (11.4) | 28.7 (1.8) | 0.21 |
| RAVLT learning, mean (SD) | 5.6 (2.6) | 5.7 (2.7) | 0.909 |
| RAVLT forgetting, mean (SD) | 3.4 (3.1) | 3.9 (3.2) | 0.301 |
| RAVLT percent forgetting, mean (SD) | 37.4 (38.1) | 39.1 (33.3) | 0.563 |
| MoCA score, mean (SD) | 24.8 (3.1) | 26.0 (3.4) | 0.112 |

Abbreviations: VA, Vaccine accepted; VH, Vaccine hesitant; MMSE, Mini-Mental State Exam; ADAS-cog, Alzheimer's Disease Assessment Scale–Cognitive Subscale; RAVLT, Rey Auditory Verbal Learning Test; MoCA, Montreal Cognitive Assessment

medial orbitofrontal, pars opercularis, pars orbitalis, pars triangularis, rostral middle frontal, superior frontal, precentral gyrus, caudal anterior cingulate, rostral anterior cingulate, isthmus cingulate, insula, parahippocampal, posterior cingulate, bankssts, entorhinal, inferior temporal, middle temporal, superior temporal, temporal pole, transverse temporal, inferior parietal, paracentral, postcentral, precuneus, superior parietal, supramarginal, pericalcarine, pericalcarine, fusiform, cuneus, lateral occipital, lingual, and hippocampus. We obtained the imaging data of the latest visit prior to the pandemic for each subject.

Cognitive assessments

The Mini-Mental State Examination (MMSE) which included 30 questions to measure the cognitive status was performed by ADNI staff during the last visit. We also obtained the Montreal Cognitive Assessment (MoCA) score of participants which included 30 questions and was used to assess dementia. Also,

the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) to evaluate the level of cognitive dysfunction, and the Rey Auditory Verbal Learning Test (RAVLT) to assess verbal learning and memory. The cognitive scores and volumetric data were obtained at the same visits.

Statistical analysis

The SPSS version 22 (BM Corp., Armonk, NY, USA) was used for statistical analysis. To check the normality the Kolmogorov-Smirnov test was performed. The demographical characteristics were compared using a t-test for parametric variables and Mann–Whitney U-test for non-parametric variables. First, to investigate the significant difference in cortical and subcortical volume between VA and VH groups, we identified potential regions with a P-value lower than 0.2 in ANOVA models. Then we entered the potential region and cognitive scores in ANCOVA models adjusted for the effect of age, years of education, and sex was conducted. Next, we measured the association between significant regions and cognitive scores using partial correlation controlled for age, years of education, and sex. In order to address type I error due

to multiple comparisons, the Benjamini-Hochberg method was applied. The results were considered significant with P-value<0.05.

Results

Comparison of clinical and demographical characteristics

A total of 221 subjects with a mean age of 63.7 ± 6.1 were entered into the analysis. There was no significant difference in age, years of education, sex, and marital status between VA and VH groups. The cognitive scores and volumetric data were obtained at 1.3 ± 1.1 years before the vaccination decision. The demographic of participants are detailed in Table 1.

Cognitive status

We investigated the difference in cognitive status between VA and VH groups. Our ANCOVA analysis demonstrated that there was no significant difference in cognitive status measured by MMSE, MoCA, ADAS-cog, and RAVLT between VA and VH groups ($P>0.05$) (Table 2).

Volumetric analysis

Our initial analysis identified seven potential regions with $P<0.2$ including left pars orbitalis, left precentral, left transverse temporal, right paracentral, right pars opercularis, right caudal anterior cingulate, and right isthmus cingulate (Table 3). To examine whether there is a difference in cortical or subcortical volume between the VA and VH group, the ANCOVA models adjusted for age, sex, and years of education were used for mentioned potential regions. The analysis showed that VA subjects had significantly higher left pars orbitalis ($P: 0.013$, $F: 6.773$), left precentral ($P: 0.042$, $F: 4.402$), right caudal anterior cingulate ($P: 0.044$, $F: 4.287$) and right isthmus cingulate ($P: 0.013$, $F: 6.702$) volume compared to the VH group (Table 3, Figure 2). There was no significant difference in other cortical and subcortical regions.

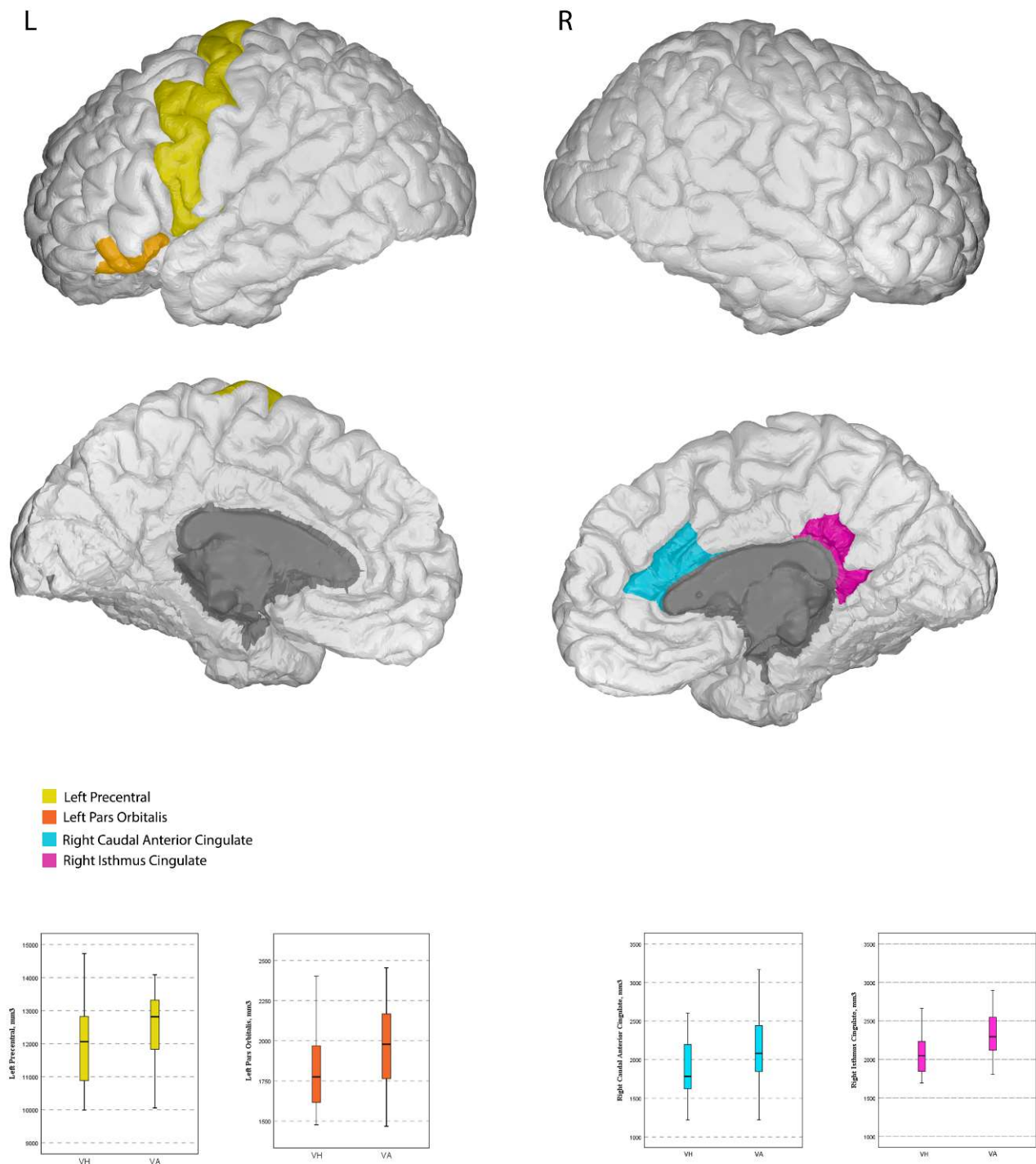


Figure1. The significant brain regions are represented

Our correlational analysis showed a significant correlation only between MoCA score and right caudal anterior cingulate ($P: 0.036$, $r: 0.384$).

Discussion

In the present study, I aimed to investigate the differences in brain regions volume between those who accepted COVID-19 vaccination and those are hesitant about being vaccinated. Our findings demonstrated that COVID-19 vaccine acceptance is associated with higher pars orbitalis, precentral, caudal

anterior and isthmus cingulate (Figure 1). However, there was no difference in cognitive status measured by MMSE.

Currently, vaccine hesitancy has become a crucial issue around the world while there is a need for a high percentage of immunization to partially control the COVID-19 spreading. Refusing the getting vaccinated is more worrying, especially in older adults which have higher rates of mortality and experience more severe disease course due to COVID-19 similar to other infections as well (9). Previous studies linked the higher cognitive ability to more health-protective behavior

Table3. Significant results of ANCOVA models

| Brain region | ANOVA | | ANCOVA (adjusted) | |
|---|-------|--------------|-------------------|--------------|
| | F | P value | F | P value |
| Left Pars Orbitalis, mean (SD), mm3 | 3.371 | 0.073 | 6.773 | 0.013 |
| Left Precentral, mean (SD), mm3 | 2.804 | 0.101 | 4.402 | 0.042 |
| Left Transverse Temporal, mean (SD), mm3 | 3.108 | 0.84 | 3.721 | 0.060 |
| Right Paracentral, mean (SD), mm3 | 4.433 | 0.041 | 4.045 | 0.051 |
| Right Pars Opercularis, mean (SD), mm3 | 4.177 | 0.047 | 2.842 | 0.099 |
| Right Caudal Anterior Cingulate, mean (SD), mm3 | 4.08 | 0.049 | 4.287 | 0.044 |
| Right Isthmus Cingulate, mean (SD), mm3 | 5.832 | 0.02 | 6.702 | 0.013 |

Significant results are bolded

The ANCOVA model adjusted for effect of age, years of education, and sex

as well as COVID-19 vaccination (11-13). However, there is less known about the neurobiology basis of this behavior. Various explanations can be suggested for the relation between vaccine intention and cognition for example individuals with higher cognitive performance are better at obtaining, processing, and responding to health advice (25). Although, during this pandemic, there is a huge number of false health advice across social media and news outlets which was never seen before. However, people had to weigh up, synthesize, acquire, and deploy this wide range of preventive information to reduce their risk of infection which is vary according to their level of cognitive performance (26). Also, the various level of cognitive function can be linked to the different brain structural measures importantly in the regions that are responsible for cognitive process (17). Based on our findings, the difference in frontal and cingulate regions may be responsible for the intention to vaccination and more generally in health-protective behavior.

It is well-known that the cingulate cortex processes cognitive, emotional, and social information (27). The cingulate is part of the limbic system which is divided into anterior and posterior parts. The anterior cingulate receives inputs from the amygdala and orbitofrontal cortex while the posterior cingulate receives from the parietal cortex and hippocampus (28). Based on previous studies different functions are described for cingulate and it is difficult to define an exact role for this area. However, several functions were reported for the cingulate including attention, anticipation, learning, motivation, working memory, reward assessments, and morality (27). Also, impairment in cingulate regions is commonly reported in Alzheimer's disease, autism, depression, and schizophrenia (29).

Also, our findings showed that those who are hesitant about COVID-19 vaccination have smaller pars orbitalis which is also known as the orbitofrontal cortex and is part of the inferior frontal gyrus. Based on previous studies, the orbitofrontal cortex is involved mainly in decision making, for example, choosing to do exercise or hang out with a friend

(30). It was found that people with damaged orbitofrontal cortex often make poor life choices and also sometimes observed that they are impulsive and unable to socially navigate the world (31).

While we found brain structural differences between VA and VH subjects, there was no difference in cognitive status. A reason for this finding can be that the vaccine-hesitant people may have only a slightly lower cognitive function in one cognitive domain. Therefore, the cognitive status should be measured by more precise and sub-domain tests to find significant differences. However, Batty et al. study demonstrated that those with lower cognitive scores were more likely to be vaccine-hesitant (11).

According to my findings, elderly individuals who accepted COVID-19 vaccination had higher volumes of cingulate and frontal regions. The proposed function for the cingulate and orbitofrontal cortex may explain this finding (27, 29). However, such health protection behavior is a complex task including knowledge, decision-making, assessing rewards, and planning which require involving multiple cognitive domains. After all, my findings complete the results of previous studies which demonstrated that cognitive performance is involved in vaccine acceptance and more general health protection behaviors and lower cingulate and orbitofrontal cortex volume may play an important role in less intention to vaccination (11, 14, 32). However, these results should be interpreted carefully because only elderly adults entered and the aging process potentially could be an effecting factor while investigating the brain structural measures.

While this study has its strength including examining multiple brain regions and the timing of data collection, there are also some limitations. First, our sample size consisted of elderly adults and the results cannot be attributed to the general population. Second, the sample size was small and further studies with a larger sample size should be conducted to confirm the findings. Third, multiple factors could influence the adherence to the vaccination including the local

microenvironments, a family story of vaccination, government interventions, and social media which were not adjusted in our study.

In conclusion, this finding demonstrated that in the era of complicated decision-making due to social media reports, elderly adults with smaller frontal and cingulate regions are more likely to be vaccine-hesitant. These findings can highlight the link between cortical regions and health-protective behaviors such as taking up the offer of vaccination. Future investigation should be performed to investigate the neurobiology basis of this behavior.

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Declarations

Funding

We do not have any financial support for this study.

Conflict of interest

The authors have no conflicts of interest to disclose.

Availability of data

The datasets analyzed during the current study are available upon request with no restriction.

Code availability

Not applicable

Ethical approval

The data in this paper were obtained from the ADNI database (adni.loni.usc.edu). It does not include any examination of human or animal subjects.

Consent for publication

This manuscript has been approved for publication by all authors.

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