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Research Article

Greater Executive Dysfunction Associated with mRNA SARS-Cov-2 Vaccines in Patients with Alzheimer's Disease

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Abstract

There is increasing evidence that mRNA vaccines for SARS-CoV-2 contribute to vascular system stress and dysfunction. Hence, there is a possibility that these vaccines may be associated with frontal/subcortical dysfunction and that patients with Alzheimer's disease (AD) may be particularly vulnerable. The present investigation sought to explore this possibility, predicting that patients with AD who had received either the Moderna or Pfizer vaccine would exhibit significantly worse performance on indices of executive functioning as compared to those who had not taken any vaccine. Measures of executive functioning were administered to a sample of 32 patients with AD that had taken either the Moderna or Pfizer vaccine and 32 age, education, and treatment matched patients with AD who had not taken any vaccine. The results of separate independent samples t-tests indicated significantly lower performance on two of the four indices of executive functioning and a measure of general cognitive functioning in patients who had taken the Moderna or Pfizer vaccine. The findings suggest that the mRNA vaccines had the essential effect of advancing disease by approximately a year in patients with AD. Further research is needed to determine if these same effects are found in normal, healthy individuals.

Keywords: mRNA; Moderna; Pfizer; Executive; Neuropsychological; Alzheimer's; Brain Cerebrovascular, SARS-CoV-2, vaccine

Introduction

Greater executive dysfunction associated with mRNA SARS-CoV-2 vaccines in patients with Alzheimer's disease.

A recent investigation reported by Avolio, and colleagues examined the effect of the SARS-CoV-2 spike protein on pericytic cardiac signaling and function. The findings indicated that using a SARS-CoV-2 isolate from the pandemic the virus was not found to infect cardiac vascular pericytes in vitro but that recombinant spike (S) protein was associated with functional alterations in cardiac pericytes. A number of effects were reported, including diminished ability to support endothelial cells and secretion of proinflammatory molecules. The authors concluded that circulating S proteins may contribute to microvascular injury [1]. Although there are differences between vaccines that use recombinant DNA technology as opposed to vaccines that use mRNA technology, the ultimate goal and effect of these vaccines is the same. Both types of vaccines are designed to cause an immune response from the biosynthesis of the S protein. Hence, the possibility exists that both types of vaccines may contribute to microvascular injury.

The potential deleterious effect of SARS-CoV-2 vaccines on pericytes carries serious implications for cerebral functioning given the critical role pericytes have in the neurovascular unit. Research has demonstrated that pericytes regulate cerebral blood flow [2,3]. Loss of blood flow and neuronal loss has followed pericyte ablation

[4]. Additional research has reported cerebrovascular dysregulation, including reduced global and individual cerebral blood flow, as well as reduced number of neurons in pericyte-deficient mice [5]. Bell and colleagues proposed that loss of pericytes may result in cerebrovascular damage by reducing brain microcirculation or by diminishing the blood-brain barrier [6].

The possibility of vaccines based on mRNA technology to cause or contribute to microvascular injury is supported by numerous case reports of thrombocytopenia following administration of either the Pfizer or Moderna vaccines [7-10]. Thrombotic thrombocytopenia following the Pfizer vaccine [11] and the Moderna vaccine [12] have also been reported. Other researchers have reported increased risk of arterial thromboembolism and ischemic stroke following the Moderna vaccine [13]. These reports and findings are concerning given that patients with immune thrombocytopenia (ITP) are known to have increased risk of ischemic stroke or transient ischemic attack [14]. Structural imaging has also revealed findings consistent with small vessel ischemic disease in patients with ITP [15].

Thiele and colleagues examined differences between the AstraZeneca and Pfizer vaccines in frequency of positive anti-PF4/polyanion antibody tests. A total of 281 health care workers received either a single dose of the AstraZeneca vaccine or two doses of the Pfizer vaccine separated by 21 to 28 days. The results indicated that 6.8% of all participants tested positive for anti-PF4/polyanion antibodies following vaccination, including 8.0% of these receiving the AstraZeneca vaccine and 5.6% of those receiving the Pfizer vaccine [16]. The finding of positive anti-PF4/polyanion antibodies following Pfizer vaccination raises a concern for not only vaccine-induced immune thrombotic thrombocytopenia but also other vascular injury and stress. The finding of only 5.6% testing positive may seem trivial. However, according to the Centers for Disease Control a total of 177,708,060 individuals have been fully vaccinated with either the Pfizer or Moderna vaccines as of November 4, 2021. Given the findings of Thiele and colleagues a total of approximately 9,952,000 individuals would then test positive for anti-PF4/polyanion antibodies.

Risk factors for small vessel ischemic disease have also been reported following the Pfizer and Moderna vaccines. A recent study investigating cardiovascular adverse events following the Pfizer or Moderna vaccines reported 16.12% of individuals experienced tachycardia following the Pfizer vaccine. Tachycardia was reported in 15.75% of individuals following the Moderna vaccine and 7.25% experienced increased blood pressure [17]. Other researchers have also reported hypertension following mRNA vaccines [18,19]. Fazio and colleagues reported that case of a 40-year-old woman who experienced severe headache, high fever, and musculoskeletal pain following a booster of the Pfizer vaccine. Subsequent laboratory panels revealed what was considered severely elevated d-dimer results [20]. Certainly, this case report does not in and of itself directly support any causal relationship between vaccination and elevated d-dimer, but the finding does raise concern that the vaccine may be associated with increased clotting.

Additional evidence for increased clotting following mRNA vaccination is provided by the results of an investigation of the risk for retinal vascular occlusion after mRNA vaccination [21]. Li and colleagues sought to determine if the Moderna and Pfizer mRNA vaccines were associated with increased risk for retinal vascular occlusion, including central and branch retinal vein occlusion as well as central and branch retinal artery occlusion. The sample included a total of 745,041 vaccinated individuals and 3,874,458 unvaccinated individuals. Individuals with confirmed COVID-19 diagnosis were excluded as were individuals who were taking antiplatelet, anticoagulant, diuretic, contraceptive, or antihemorrhagic medications. The findings indicated that overall risk for retinal vascular occlusion in the individuals who were vaccinated was 2.19 times higher than that of individuals who were unvaccinated. The finding of increased retinal vascular occlusion following mRNA vaccination raises a concern that similar processes and effects may be happening in other systems, such as the cerebrum. To the extent that this might be happening in the brain it seems reasonable to conclude that this would disrupt brain functioning.

Given the aforementioned potential effects of mRNA vaccines on vascular system structure and function there exists a possibility that these vaccines may be associated with cerebral dysfunction affecting higher cortical functions, particularly executive functioning. To the extent that these mRNA vaccines contribute to small vessel disease executive functioning will be impaired. An association between the presence and extent of cerebral microbleeds and mild cognitive impairment in patients with hypertension has been reported, in the absence of stroke or transient ischemic attack [22]. Executive functioning in particular has been associated with cerebral microbleeds [23,24] and cerebrovascular disease [25-27], even in cognitively intact elderly individuals [28,29].

The potential effect of mRNA vaccines on causing or contributing to cerebrovascular disease and the subsequent impact on executive functioning may be more pronounced in patients with diseased brains, such as those with Alzheimer's disease (AD). White matter hyperintensities and microinfarcts have been reported to be associated with increased risk of AD [30]. Others have also reported an association between AD and cerebrovascular disease [31,32]. Laing and colleagues reported that among patients with AD there is an association between increased white matter hyperintensities and high plasma tau concentration [33].

Based on the aforementioned research there exists strong reason to suspect that mRNA vaccines may affect frontal/subcortical functioning and that this may be manifested by executive dysfunction. Further, these effects may be particularly evident in patients with AD. However, there have been no published studies seeking to examine whether such associations exist. Hence, the purpose of the present investigation was to determine if the mRNA vaccines (Moderna and Pfizer) are associated with frontal/subcortical dysfunction in patients with AD as evidenced by performance on tests of executive functioning. The prediction was that patients who had received either the Moderna or the Pfizer vaccine would exhibit significantly worse performance on tests of executive functioning as compared to patients who were unvaccinated.

Methods

Sample

The sample consisted of 64 patients who were diagnosed with probable Alzheimer's disease (11 men and 53 women) with an average education of 12.78 years (SD = 2.24) and an age range of 67 to 92 years (M = 80.30, SD = 5.75). Scores on the Mini Mental Status Exam ranged from 12 to 26 (M = 19.72, SD = 3.38). The diagnosis of AD was based on a thorough neuropsychological evaluation and the sample was drawn from patients who were referred to Murfreesboro Medical Clinic for a neuropsychological evaluation for memory problems. Patients diagnosed with probable AD met NINDS-ADRDA criteria. None of the patients had tested positive or been diagnosed with SARS-CoV-2 prior to the study. The data were collected prior to the availability of a booster and hence all patients received no more than the initial two doses, with two patients receiving only one dose.

Instruments

Controlled Oral Word Association Test: The Controlled Oral Word Association Test (COWAT) is a test of verbal fluency that requires the patient to name as many words as possible that begin with a specified letter (F, A, and S). Patients were given 60 seconds per letter to generate as many words as possible. However, the words cannot include proper nouns, numbers, or stem words with different endings such as top followed by tops, topping, topped. The dependent variable of interest consisted of the total number of words produced.

Digit Symbol: The Digit Symbol (DS) test is a subtest of the Wechsler Adult Intelligence Scale – III (WAIS-III) and is a measure of attention and processing speed. The test pairs nine digits (1 through 9) with nine different symbols in a key code at the top of the page. The remainder of the page consists of a series of boxes with the top portion containing the digits in a pseudorandom fashion and the boom portion being empty. The task requires the patient to write the symbol for each digit in the empty portion of the box. The dependent variable of interest in this study consisted of the total number of boxes corrected completed.

Geriatric Depression Scale: The Geriatric Depression Scale (GDS) [34] is a 30 item self-report questionnaire designed for use with older populations. Participants are asked to respond either "yes" or "no" to each item, with a range of possible scores from 0 to 30. The dependent variable of interest was the total raw score.

Mini Mental Status Exam: The Mini-Mental State Examination (MMSE) [35] is a screening test used to assess general cognitive functioning. Areas of functioning assessed include orientation, registration, attention, recall, working memory, language, and construction or drawing ability. Possible scores range from 0 to 30, with higher scores reflecting improved mental status, and the dependent variable of interest was the raw score.

Stroop Color-Word Test: The Stroop Color-Word Test (SCWT) [36] consists of three conditions. The first condition (Word Reading) consists of the words blue, green, and red being printed on a page and printed in black ink. A total of 100 words are presented on the page in five columns and in a random order. The patient is asked to read the words aloud going down each column as fast as possible. The second condition (Color Naming) consists of a series of "xxxx" printed in three different ink colors, blue, green, and red. There are 100 of these printed on the page in five columns and in random order. The patient is asked to state the color of ink as quickly as possible. The last condition (Color-Word) consists of the words blue, green, and red printed in a dissonant color ink (either blue, green, or red). As before there are a total of 100 words printed in five columns. The patient is asked to state the color of ink and not to read the word as quickly as possible. For each of the three conditions the patient is given 45 seconds to read as many as possible. The dependent variable of interest in this study consisted of the raw score for the Color-Word condition.

Trail Making Test: The Trail Making Test (TMT) consists of two parts. Part A is comprised of encircled numbers, 1 through 25, spread in a pseudorandom order across a page. The participant is instructed to draw lines connecting the numbers in order as fast as possible and without picking up the pencil. Part B is comprised of encircled numbers, 1 through 13, and letters, A through L, spread across a page in a pseudorandom order. The participant is instructed to draw lines alternately connecting the numbers and letters, each in order, as fast as possible and without picking up the pencil. The dependent variables of interest consisted of the raw scores for both Part A and Part B.

Design

This study was completely retrospective in nature and was approved by the Middle Tennessee State University Institutional Review Board. The study was conducted maintaining the ethical principles of the American Psychological Association. The participants all completed a thorough neuropsychological evaluation for diagnostic determination of Alzheimer's disease. The aforementioned dependent variables were all administered as part of this evaluation and were administered in a pseudorandom fashion. Administration of all tests adhered to standardized protocols for the tests. As part of the evaluation the patients were asked to indicate if they had received a COVID-19 vaccine and to indicate which vaccine they received if they had. Only patients who indicated receiving the Moderna (N = 22) or Pfizer (N = 10) vaccines were included in the study. The average time between the initial mRNA vaccine dose and the time of testing of executive functioning was 120.22 days (SD = 65.40) days, with a range of 14 to 230 days. Unfortunately, the date of vaccination was not available for 14 of the patients, though the type of vaccination and number of injections was known. Also, all data was collected within the first year of the vaccines being made available, with all data being collected in 2021. Hence, all participants had received their vaccine within a year of this study.

A comparison group of patients diagnosed with Alzheimer's disease who had not received any COVID-19 vaccine was also used. A matching process was used to control known potential confusion. Specifically, patients with AD who received either the Moderna or Pfizer vaccine were matched to patients with AD who had not received any vaccine on three different variables, age, education, and treatment status. To match on age a difference of no more than ±5 years was used as the matching standard. This matching

standard is consistent with normative studies and data that often use 10 years as an age range. The criteria for matching on education included 0 to 8 years of education, 9 to 12 years of education, and 13 or more years of education. This matching standard is also consistent with many normative studies on neuropsychological functioning. Finally, the matching standard for treatment status focused on commonly used treatments for dementia, including donepezil, rivastigmine, and memantine. Specifically, the patients were matched on which medications or combination of medications they were currently taking. There were no patients taking galantamine, tacrine, or donepezil/memantine (Namzaric). The matching process was completed while being blinded as to performance on neuropsychological tests.

Results

Preliminary Analyses

Preliminary analyses were conducted to determine the success of the matching process. Regarding age, the vast majority of the matched patient pairs were no more than 2 years apart (N = 23). The patients were separated by no more than 2 years of education, with the majority being perfectly matched on years of education (N = 22). All patients were perfectly matched on treatment status. For each group there were 7 patients taking donepezil, 2 patients taking memantine, 2 patients taking both donepezil and memantine, and 21 who were not taking any treatment for dementia.

A series of two-tailed independent groups t-tests was conducted to ensure no differences existed between the groups in age and education. A separate t-test was also conducted on scores from the GDS to ensure there was no difference in depression between the groups and therefore rule out this additional potential confounding variable. The results of these analyses indicated no significant differences between the groups in age, education, or GDS score (see Table 1).

Given that the hypothesis was predicated on the potential effect of the mRNA vaccines on affecting vascular system and functioning an additional analysis was conducted to determine if the groups differed in risk for small vessel ischemic disease. The number of major risk factors for small vessel ischemic disease present for each patient was determined. The major risk factors included hypertension, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, diabetes, and atrial fibrillation. The results of a two tailed independent groups t-test revealed no significant difference between the groups in the number of risk factors present (see Table 1).

Primary Analyses

It should be noted at the outset that some patients did not receive all of the neuropsychological tests. Specifically, three patients did not receive the SCWT, five patients did not receive the TMT, and seven patients did not receive the DS test. The vast majority of the patients received all neuropsychological tests. Specifically, a total of 86% of the total sample received all neuropsychological tests, including 82% of the patients in the vaccinated group and 95% of the patients in the not vaccinated group. Also, there were many patients for whom the TMT Part B was discontinued due to reaching a maximum time limit of five minutes (N = 23). Therefore, TMT Part B was not included in subsequent analyses.

The data from neuropsychological testing was evaluated using a series of one-tailed independent groups t-tests. Based on Levene's test for equality of variances the differences in variances for the two groups was noted to differ significantly for the TMTA and DS measures. Hence, for these analyses equal variances not assumed results were used. The results indicated that a significant difference existed between the groups on the MMSE, TMT Part A, and DS tests. The results from analysis of the COWAT and SCWT tests were not significant. Effect sizes were calculated for the significant differences using Cohen's d. The effect sizes ranged from medium to large [Table 1].

Secondary Analyses

The finding of a significant difference in MMSE scores between the mRNA and No mRNA groups may raise a concern that lower general cognitive functioning might explain the results on the other, more specific, tests of executive functioning. Hence, a series of secondary analyses were completed controlling for MMSE by entering this variable as a covariate in the analyses. The results of a series of ANCOVAs indicated that a significant difference continued to exist for both the TMT Part A and for the DS tests. The effect sizes ($\eta 2$) were large [Table 2].

Table 1: Demographic information and results from initial and primary analyses.

Initial Analyses	mRNA	No mRNA	t-test	d
Age	80.31 (6.03)	80.28 (5.54)	t (62) = .022, p = .983	---
Education	12.88 (2.18)	12.69 (2.32)	t (62) = .333, p = .740	---
GDS	7.70 (6.28)	7.65 (5.81)	t (59) = .035, p = .972	---
Risk Factors	1.81 (.86)	1.53 (.84)	t (62) = 1.32, p = .191	---
Primary Analyses	**mRNA**	**No mRNA**	**t-test**	**d**
MMSE	18.78 (3.47)	20.66 (3.05)	t (62) = -2.294, p = .0125	0.57
COWAT	22.44 (9.87)	24.53 (10.96)	t (62) = -.803, p = .2125	---
SCWT	13.27 (9.15)	14.58 (9.29)	t (59) = -.556, p = .290	---
TMTA	247.93 (102.63)	236.26 (70.91)	t (57) = 2.712, p = .005	0.7
DS	27.04 (14.82)	37.67 (9.67)	t (55) = -3.238, p = .0015	0.85
Note: Means are provided with standard deviations in parentheses.				

Table 2: Results from ANCOVAs with MMSE as the covariate.

Secondary Analyses	mRNA	No mRNA	F	η^2
COWAT	22.79 (1.88)	24.18 (1.88)	F (1, 61) = .261, p = .611	---
SCWT	14.05 (1.63)	13.82 (1.61)	F (1, 58) = .01, p = .921	---
TMTA	78.67 (6.45)	59.88 (6.12)	F (1, 56) = 4.332, p = .042	0.25
DS	28.43 (2.25)	36.42 (2.13)	F (1, 54) = 6.425, p = .014	0.29
Note. Estimated marginal means are provided with standard error in parentheses.				

Discussion

Based on evidence that mRNA vaccines may cause microvascular injury and therefore frontal/subcortical dysfunction it was predicted that patients with AD who received either the Moderna or Pfizer vaccines would exhibit worse performance on measures of executive functioning. The results of this investigation provide partial support for this hypothesis. Specifically, patients with AD who received either vaccine were found to exhibit significantly worse performance on the Digit Symbol subtest of the WAIS-III and Part A of the Trail Making Test, with the effect sizes for these differences being medium for the TMT data and large for the DS data. Performance on the DS subtest has been associated with a frontoparietal network based on fMRI data [37] as well as patients with severe white matter lesions [38]. Performance on the DS subtest has also been found to be significantly correlated with other indices of executive functioning, such as the SCWT [39,40], the Letter-Number Sequencing subtest of the WAIS-III [41], and the Wisconsin Card Sorting Test [40]. Likewise, performance on Part A of the TMT has been associated with tests of purported executive functioning, including phonemic verbal fluency and the SCWT [42]. Patients with focal frontal lobe lesions as compared to lesions at other regions have demonstrated lower performance on TMT Part A [43,44]. Hence, the findings of the present investigation provide some support for the hypothesis that patients with AD who received the mRNA vaccines would exhibit worse performance on purported indices of executive functioning, which then suggests greater frontal/subcortical dysfunction.

A significant difference between the groups was also found for the MMSE. Specifically, the present findings indicated that patients who had taken the Moderna or Pfizer vaccine exhibited a significantly lower MMSE score than those who had not taken any vaccine, with the effect size indicating a moderate effect. The MMSE is a commonly used instrument to assess general cognitive functioning and often as a screening instrument for dementia. Further, many clinicians use the MMSE to gauge progression of disease. The general rule of thumb is that patients are expected to decline about 2 points per year on the MMSE. Average rates of decline for scores on the MMSE in patients with AD have ranged from a low of about 1.5 points per year [45] to a high of about 2.8 points per year [46,47]. Hence, the difference of 1.88 found in the present study represents the equivalent of approximately a year of cognitive decline.

The present findings carry important implications not only for the potential advancement of disease in patients with AD but also their ability to perform instrumental activities of daily living (IADL). Executive dysfunction predicts impairment in IADLs in patients with AD [48]. Further, patients with AD who exhibit executive dysfunction perform worse not only in IADLs but also exhibit more frequent symptoms of psychosis [49]. Additionally, there are implications for long-term care. Loss of ability to perform IADLS is an important predictor of placement in managed care [50,51].

The sample of the present study was comprised of patients with AD. Patients with AD may be particularly vulnerable to the effects of the Moderna and Pfizer vaccines on vascular system and function given the potential role of pericytes in the pathogenesis of AD [52,53]. However, to the extent that pericytes are involved in the pathogensis of Alzheimer's disease, individuals who have received the Moderna or Pfizer vaccines may be at increased risk for developing AD later in life. Certainly, the present data do not provide direct support for this proposition but given the demonstrated effect of these vaccines on frontal/subcortical functioning this possibility is worth exploring. As an initial step, though, research needs to be conducted focusing on determining whether the present findings are also observed in neurologically intact, healthy individuals.

There have been numerous studies published examining the safety of the Moderna and Pfizer vaccines. However, these investigations have focused on major adverse events, and none have examined potential neurocognitive effects. Hence, the present investigation represents a first report examining the effects of the Moderna and Pfizer vaccines on frontal/subcortical functioning and the resulting impairment in executive functions. However, this study is certainly not without limitations that should be carefully considered. The present investigation used a quasi-experimental design and not the gold standard double blind placebo-controlled design. Major known confounding variables were controlled in this investigation, such as age, education, and treatment status. Additionally, there were no differences between the groups in depression or risk factors for cerebrovascular disease.

However, given the lack of randomization there cannot be absolute certainty that some unknown confounding variable accounted for the findings. Although a causal relationship cannot be determined based on the present findings the current findings do provides evidence for a moderately strong relationship between the mRNA vaccines and frontal/subcortical dysfunction as evidenced by performance on tests of executive functioning. Unfortunately, it is highly unlikely that double blind randomized designs would be possible at this point given the prevalence of vaccine hesitancy and that individuals who have not been vaccinated are not likely to alter their opinion and become vaccinated [54]. However, replication

of the present findings in other patient populations, age groups, and among the healthy would strengthen the present findings and further support that an association exists between the mRNA vaccines and frontal/subcortical dysfunction.

Data Availability Statement

The data will be made available on reasonable request.

Acknowledgement

None.

Conflict of Interest

The author reports there are no competing interests to declare.

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