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The association between head motion during functional magnetic resonance imaging and executive functioning in older adults

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Abstract

Minimizing head motion during functional magnetic resonance imaging (fMRI) is important for maintaining the integrity of neuroimaging data. While there are a variety of techniques to control for head motion, oftentimes, individuals with excessive in-scanner motion are removed from analyses. Movement in the scanner tends to increase with age; however, the cognitive profile of these "high-movers" in older adults has yet to be explored. This study aimed to

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Author contributions

HH, CH, and AW contributed to the conception and design of the study; HH extracted the data and performed the statistical analyses. HH and CH wrote the first draft of the manuscript. EP, GH, SW, SD, GA, MM, RC, and AW were involved in project administration. All authors contributed to manuscript revision, read, and approved the submitted version.

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.

assess the association between in-scanner head motion (i.e., number of “invalid scans” flagged as motion outliers) and cognitive functioning (e.g., executive functioning, processing speed, and verbal memory performance) in a sample of 282 healthy older adults. Spearman’s Rank-Order correlations showed that a higher number of invalid scans was significantly associated with poorer performance on tasks of inhibition and cognitive flexibility and with older age. Since performance in these domains tend to decline as a part of the non-pathological aging process, these findings raise concerns regarding the potential systematic exclusion due to motion of older adults with lower executive functioning in neuroimaging samples. Future research should continue to explore prospective motion correction techniques to better ensure the collection of quality neuroimaging data without excluding informative participants from the sample.

Keywords

Head motion; Executive functioning; Inhibition; Set-shifting; Older adults

1. Introduction

A key component of brain functional magnetic resonance image (fMRI) processing is identifying and removing scans laden with head motion (Wylie et al., 2014). Controlling for motion is a crucial step in retaining validity that data within a voxel corresponds to a particular brain region throughout the duration of the scan (Wylie et al., 2014). Head motion disrupts the MR signal and severely degrades the quality of the scan (Friston et al., 1996). Head motion is particularly disruptive in fMRI, as these analyses rely on correlating fluctuations in blood oxygen level dependent (BOLD) signal over a time series. Head motion disrupts the BOLD signal associated in primary and neighboring voxels (Power et al., 2012). This can result in erroneous correlations (motion artifacts) when assessing resting-state fMRI data following a pattern of increased correlation between closely spaced voxels and decreased correlation between spatially distant voxels (Power et al., 2012). Similarly, on a network level, head motion has been associated with reduced functional coupling of distributed networks (e.g., default mode and frontoparietal control networks) and increased coupling for local networks (van Dijk et al., 2012; Satterthwaite et al., 2012). Head motion also affects the validity of task-based functional data, particularly when performing more challenging in-scanner tasks (Wylie et al., 2014).

Current fMRI data processing practices attempt to mitigate the effects of head motion in two major ways: prospectively and retrospectively. Briefly, prospective motion correction methods attempt to track motion in real-time and adjust the field of view and gradient directions accordingly (Maclaren et al., 2013). Retrospective motion correction occurs at the image processing stage, and includes techniques of spatial realignment, scrubbing outlier scans (e.g., framewise displacement >0.9 mm; Power et al., 2012, 2014; Siegel et al., 2014), regression of motion estimates (Friston et al., 1996), and temporal band-pass filtering. A third strategy to reduce head motion before data acquisition is through the use of foam pads and restraints, although the efficacy of this method is variable (Jolly et al., 2020; Krause et al., 2019; Maclaren et al., 2013). While head motion appears to be ubiquitous in human fMRI, several studies suggest that the level of head motion may reflect a neurobiological

trait more so than a technical artifact (Couvy-Duchesne et al., 2014; Seto et al., 2001; Zeng et al., 2014). For example, individuals with greater head motion showed reduced distant functional connectivity in the default mode network (Zeng et al., 2014), a network implicated in a variety of psychiatric and neurological diseases, such as Alzheimer's disease (Fox and Greicius, 2010; Greicius, 2008). Further, the propensity for head motion remains stable within individuals across separate MRI sessions, suggesting amount of movement is a reliable trait characteristic (Zeng et al., 2014; Geerligs et al., 2017). These findings suggest that the severity of head motion may be associated with brain function integrity, and therefore, cognitive functioning.

Previous research has shown that cognitive status is associated with in-scanner head motion across the lifespan and in clinical populations. Geerligs et al. (2017) demonstrated that participants across the lifespan (ages 18–88) with high head motion scored lower on a test of fluid intelligence and had more variable reaction times on a choice reaction time test. A comprehensive, large-scale study in young adults demonstrated that different subgroups of movers could be identified using 36 motion summary measures and distinguished by anthropometric and cognitive measures (Bolton et al., 2020). For example, subjects who had significant motion across all spatial degrees of freedom, time bins, and sessions had larger weight, elevated blood pressure, greater sleep issues, reduced cognitive flexibility, inhibitory control, language abilities, processing speed, theory of mind, and working memory. These findings suggest that motion in fMRI can be associated with behaviorally relevant information. Importantly, the amount of in-scanner head motion increases with age (Madan, 2018; Pardoe et al., 2016) and can be used to discriminate between healthy older adults, those with amnestic mild cognitive impairment, and those with Alzheimer's disease, suggesting that in-scanner head motion may be diagnostically important (Haller et al., 2014). Therefore, exclusion for excessive motion may inadvertently introduce sampling bias, particularly within clinical and aging populations with brain function changes [e.g., stroke (Seto et al., 2001), multiple sclerosis (Wylie et al., 2014), non-pathological vs. pathological aging (Haller et al., 2014)].

However, no study to our knowledge has assessed the cognitive profile of healthy older adults with high in-scanner motion, particularly within domains of cognitive control. This has been explored in young adults, however, showing that more in-scanner motion was related to worse impulse control (Kong et al., 2014). In cognitively healthy aging, older adults experience further declines in cognitive control domains like working memory, inhibition, and flexibility related to changes in brain structure and function (Evangelista et al., 2021; Hausman et al., 2020; Kraft et al., 2020; Peters, 2006; Salthouse, 2010). Less cognitive control may influence an individual's capability to implement a verbal instruction (e.g., "remain still throughout the duration of a scan"), to consistently monitor their head motion, and to suppress distractions from the novel scanning environment (e.g., loud noises). Characterizing the cognitive profile of high in-scanner movers in a healthy older adult population may reveal sampling-bias with current motion control practices, as these individuals are typically removed from further analyses.

This study aims to explore the association between in-scanner motion at rest with cognitive performance in a variety of executive (inhibition, set-shifting, working memory), processing

speed, and verbal memory measures in a sample of cognitively healthy older adults. These domains were selected to target cognitive functions that typically decline in healthy aging (Salthouse, 2010, 2019). Based on prior literature in young adults (Kong et al., 2014), we hypothesize that reduced inhibition will be associated with greater in-scanner head motion compared to other areas of executive functioning (i.e. set-shifting and working memory), processing speed, and verbal memory. Systematic exclusion of these participants could skew study interpretations, as older individuals with lower executive functioning tend to have reduced integrity of activities of daily living and altered brain function connectivity (Hausman et al., 2020; Cahn-Weiner et al., 2002; Roye et al., 2020**).**

2. Materials and methods

2.1. Participants

Data were collected at baseline from participants recruited for the Augmenting Cognitive Training in Older Adults (ACT, R01AG054077) study (Woods et al., 2018). Our sample included 282 healthy older adults ranging from 65 to 88 years old (mean age = 71.6 ± 5.1; 177 females; mean education = 16.3 ± 2.4, education range = 12–21 years; Table 1) recruited at the University of Florida (n = 183) and at the University of Arizona (n = 99). Most of participants identified as White (87%), 6% as Black or African American, 2% as American Indian/Alaskan Native, 2% as more than one race, 1% as unknown or not reported, and <1% as Asian or Native Hawaiian or other Pacific Islander. 7% of the entire sample also identified as Hispanic or Latinx. Woods et al. (2018) detail the inclusion and exclusion criteria. Participants were between the ages of 65–89, had no history of major psychiatric illness, no history of brain or head injury resulting in loss of consciousness greater than 20 min, and no formal diagnosis or evidence of mild cognitive impairment, dementia, or neurological brain disease. The Uniform Data Set (UDS) of the National Alzheimer's Coordinating Center (NACC) was used to screen for individuals with possible mild cognitive impairment (MCI) or dementia (Weintraub et al., 2009). Possible MCI was defined by 1.5 standard deviations below the mean of age-, sex- and education-adjusted norms in any of the following domains: general cognition, memory, visuospatial, executive functioning/working memory, or language. All participants were right-handed and had no contraindications for scanning (e.g., metal implants such as pacemakers, brain aneurysm clips, etc.). Individuals were not excluded if they had dental implants; however, all images were visually assessed for potential artifacts due to implants prior to analyses. Participants signed a consent form approved by the Institutional Review Boards at the University of Florida and at the University of Arizona.

2.2. Neuropsychological measures

Neuropsychological measures were administered to all participants as part of a larger cognitive battery (Table 2). Variables included in this study were chosen to reflect a cognitive profile accentuating executive functioning, but including measures of processing speed and verbal memory, as these abilities also decline with age (Salthouse, 2010).

2.2.1. Executive functioning

Set-Shifting –: The Trail Making Test Part B (TMT-B) from the NACC battery (Weintraub et al., 2009; Reitan and Wolfson, 1993) is a speeded motor-based task that asks participants to sequence alternating numbers and letters as fast as they can. Outcome variable is the amount of time it takes for a participant to complete 13 sequences correctly.

Inhibition –: The Stroop Color-Word trial (Stroop, 1935) consists of color words printed in an incongruent colored ink. Participants are asked to name the color of ink that a word is printed in, ignoring the actual word printed, requiring the inhibition of an automated response. Outcome variable is number of correct trials read in 45 s.

Working Memory –: The Digit Span Backwards subtest of the Wechsler Adult Intelligence Scale - 4th edition (WAIS-IV) (Wechsler, 2008) is a task where participants are read aloud a sequence of numbers and asked to immediately repeat the sequence in backwards order; the span of numbers increases with each correct trial.

Additionally, the Letter Number Sequencing subtest of WAIS-IV was administered as another, more challenging, measure of working memory (Crowe, 2000; Wechsler, 2008). Participants are read aloud a sequence of single numbers and letters and asked to repeat back the numbers first from lowest to highest, then the letters in alphabetical order. Outcome variables of both measures is the total number of correct trials.

2.2.2. Processing speed—For the Symbol Digit Coding subtest of the WAIS-IV (Wechsler, 2008), participants are asked to transcribe symbols to a number as quickly and accurately as possible. Outcome variable is the total amount of correctly transcribed symbols in 120 s.

2.2.3. Verbal memory—During the Hopkins Verbal Learning Test – Revised (Shapiro et al., 1999), participants are read a list of 12 words over 3 learning trials. After a 20-min delay, they are asked to freely recall as many words as possible. Target outcome variable for this study is the number of words remembered at the delay recall trial, as this variable may be more sensitive and specific to mild and major cognitive impairment (Weissberger et al., 2017; González-Palau et al., 2013).

2.3. Imaging acquisition

Motion parameters were extracted from a 6-min resting-state fMRI scan. Data were collected using a 3-T Siemens Magnetom Prisma scanner with a 64-channel head coil at the Center for Cognitive Aging and Memory at the University of Florida and using a 3-T Siemens Magnetom Skyra scanner with a 32-channel head coil at the University of Arizona. Both study sites followed the same scanning procedures and used identical sequences. Participant head motion was constrained by foam padding, and participants were provided with earplugs to reduce adverse effects of scanner noise. For acquiring resting-state data, participants were asked to rest while keeping their eyes open and focused on a fixation cross. Blood-oxygen-level dependent (BOLD) scan was acquired with an echo-planar functional protocol (number of volumes = 120, repetition time [TR] = 3000 ms, echo time [TE] = 30

ms; flip angle = 70°, 3.0 × 3.0 × 3.0 mm^3 voxels; 44 slices, field of view (FOV) = 240 × 240 mm). To assist the normalization of the resting-state functional images in the preprocessing stage, high-resolution T1-weighted 3D magnetization prepared rapid acquisition gradient echo (MPRAGE) images were collected (TR = 1800 ms; TE = 2.26 ms; 1.0 × 1.0.1 × 0 mm^3 voxels; 176 slices; FOV = 256 × 256 mm; FA = 8°; time = 3 min and 3 s).

2.4. Head motion

Imaging data were preprocessed using the default preprocessing pipeline in CONN Toolbox 18b (using MATLAB R2016b) and SPM12 (Penny et al., 2007; Whitfield-Gabrieli and Nieto-Castanon, 2012). After slice-timing correction and before normalization, CONN Toolbox uses the Artifact Detection Toolbox (ART) to identify sources of artifacts in the timeseries through a combination of thresholds on the observed global BOLD signal and estimated subject motion in-scanner (Whitfield-Gabrieli and Neito-Castanon, 2012). Using the “intermediate” settings, acquisitions were flagged as outliers with global BOLD signal changes beyond 5 standard deviations and framewise displacement greater than 0.9 mm (Fig. 1). According to CONN Toolbox’s functional connectivity methods handbook, “framewise displacement is computed at each timepoint by considering a 140 × 180 × 115mm bounding box around the brain and estimating the largest displacement among six control points placed at the center of this bounding-box faces. Global BOLD signal change is computed at each timepoint as the change in average BOLD signal within SPM’s global-mean mask scaled to standard deviation units” (Nieto-Castanon, 2020). For statistical analyses, the total number of invalid scans (i.e., outliers identified by ART using the aforementioned thresholds) were extracted for each subject. Amount of in-scanner head motion was determined by the number of invalid scans, as total viable acquisition time and proportion of valid scans is currently a common recommended criterion for determining inclusion (Van Dijk et al., 2010). Additionally, the number of invalid scans reflects both motion displacement and global signal change derived from the ART Toolbox (Nieto-Castanon, 2020).

2.5. Statistical analyses

Cases that did not have neuropsychological assessment data were dropped from analyses via list-wise deletion. Additionally, to reflect a normative healthy aging sample, participants with performance beyond ±3 standard deviations from sample mean on any cognitive measure were excluded from respective analyses. One participant was missing data on Letter Number Sequencing, five on Digit Span Backwards, five on Stroop Color-Word, five on Symbol Digit Coding, and five on HVLT delay. Additionally, one individual was considered to be an outlier on HVLT delay, two individuals were considered outliers on Stroop Color-Word performance, and two were considered outliers on Trail Making Test Part B (TMT-B) performance. This resulted in sample sizes of Letter Number Sequencing n = 281, TMT-B n = 280, Digit Span Backwards n = 277, Symbol Digit Coding n = 277, Stroop Color-Word n = 275, and HVLT Delay n = 276 for correlational analyses. All remaining participants were included in analyses regardless of degree of motion.

To control for potential site differences in the quality and acquisition of MRI data, effects of “scanner” were regressed from total invalid scans. Additionally, effects of

age and education were regressed from all neuropsychological measures before analyses, as preliminary correlation analyses suggested education and age to be associated with neuropsychological performance. Due to data non-normality and the presence of invalid scan outliers, six Spearman's Rank-Order correlations – a non-parametric version of the Pearson product-moment correlation – were performed on the unstandardized residuals of each neuropsychological measure and total number of invalid scans. Exploratory correlational analyses were run to assess the relationship between total invalid scans and demographic variables: age, sex, and years of education. All statistical analyses were performed using SPSS version 25.

3. Results

3.1. Invalid scans and cognitive performance

Spearman's Rank-Order correlational analyses revealed that the total number of invalid scans was associated with performance on tasks of set-shifting (TMT-B) and inhibition (Stroop Color-Word). Higher total number of invalid scans was related to greater amount of time to complete TMT-B ($\rho = 0.20$, $p = 0.001$; i.e., worse performance) and fewer total number of correct responses on Stroop-Color Word ($\rho = -0.16$, $p = 0.009$). Performance on measures of working memory - Letter Number Sequencing and Digit Span Backwards ($\rho = -0.07$, $p = 0.28$, $\rho = -0.06$, $p = 0.34$, respectively), on a measure of episodic memory - HVLT Delay ($\rho = -0.08$, $p = 0.21$), and on a measure of processing speed - Symbol Digit Coding ($\rho = -0.06$, $p = 0.33$) was not related to number of invalid scans (see Fig. 2). Further, higher number of invalid scans was associated with older age ($\rho = 0.17$, $p = 0.003$) but not sex ($\rho = 0.04$, $p = 0.47$) or years of education ($\rho = -0.02$, $p = 0.80$).

4. Discussion

It is common practice in functional MRI pre-processing to exclude participants if the proportion of motion flagged volumes to relatively motion free volumes results in less than 4-min of fMRI data (Van Dijk et al., 2010; Satterthwaite et al., 2013; Parkes et al., 2018). However, other researchers have postulated that removal of these "high-movement" participants from analyses may introduce systematic sampling bias, particularly in clinical populations and aging populations with differing cognitive status (Seto et al., 2001; Wylie et al., 2014; Haller et al., 2014). This is the first study to assess the cognitive associates of in-scanner movement during a resting-state fMRI scan in a large sample of cognitively healthy older adults. Cognitive tasks in this study focused on executive functioning (set-shifting, working memory, inhibition) and processing speed, as these areas typically decline with healthy aging (Salthouse, 2010) and are associated with in-scanner movement in a healthy young population (Kong et al., 2014). Additionally, a brief measure of verbal memory was assessed as performance on delayed verbal memory tasks may be indicative of pathological cognitive processes (de Jager et al., 2009; Weissberger et al., 2017).

Spearman Rank-Order correlations show that high-movers in this older adult sample also were lower performers on tasks of inhibition (Stroop Color-Word trial) and set-shifting (Trail Making Test part B), partially congruent to our predictions and previous literature in healthy young populations (Kong et al., 2014). There was no association between the

number of invalid scans and two measures of working memory, processing speed, or delayed verbal memory. This suggests that better cognitive sequencing/set-shifting and inhibition skills may be in part responsible for reduced movement. While it is commonly understood that the Stroop Color-Word trial targets inhibitory control, Trail Making Test part B may also require inhibitory control and task-suppression in addition to a set-shifting component through inhibiting the automatic process of sequencing in the same set (Arbuthnott and Frank, 2010; Houghton and Tipper, 1994). Therefore, the number of invalid scans may be dependent on just the inhibitory control (i.e., active suppression of task-irrelevant information) aspect of Trail Making Test B.

The ability to suppress distractions may be critical for successful, minimal-motion scanning in an MRI environment. At the most basic level, participants are tasked to lay completely still in a restrictive, novel space while enduring loud sequencing noises. Participants must focus on the task (i.e., lying still) while suppressing these distractions and other factors like potential discomfort, pain, anxiety, and fatigue. These inhibitory processes decline with age (Persad et al., 2002; Sweeney et al., 2001) and may in part contribute to differences in managing the scanning environment between younger and older adults. For example, Gutchess and Park (2006) found that compared to younger adults, older adults had disproportionately poorer long-term memory performance in an fMRI environment when compared to a traditional laboratory setting. The authors speculate that attempting to suppress the scanning environment distractions results in a larger divided attention load, which may impact encoding.

In addition, an older adults' ability to manage their day-to-day living environment also relies on intact executive functioning. Prior research suggests that performance on the Trail Making Test part B (Cahn-Weiner et al., 2002; Bell-McGinty et al., 2002) and on a modified version of the Stroop task (Jefferson et al., 2006) is associated with functional independence and completing instrumental activities of daily living (IADLs) in older adults. Changes in IADL performance can occur long before dementia or disease onset (Perneczky et al., 2006), and difficulties with IADLs is also a risk factor for higher conversion rates from mild cognitive impairment to dementia (Jekel et al., 2015). Thus, systematic exclusion of high-movers in the scanner may result in a biased sample towards those with better executive functioning, more functional independence, and perhaps a lower risk for developing dementia; although, longitudinal research in "high-movers" would need to be conducted to investigate this notion.

Additionally, alteration in functional brain connectivity could be a contributing factor in the relationship between head motion and cognitive functioning. Older adults who are performing poorly on inhibitory cognitive measures also have altered functional connectivity of hub regions within the default mode network and poorer connectivity of the cingulo-opercular network (Zhao et al., 2020; Hausman et al., 2021). Therefore high-movers with poorer inhibitory functioning may also have disrupted functional connectivity of these resting state networks, although it is difficult to disentangle functional differences that are an artifact of movement versus true alterations in functional connectivity. However, Zeng et al. (2014) were able to demonstrate that reduced cortical connectivity between regions in the default mode network was a neurobiological trait of high-mover older adults and was

not itself an artifact of movement. Consequently, it is possible in our sample that functional connectivity could be a modulatory variable to consider in the association between high movement and reduced inhibitory functioning.

Another modulation factor to consider is brain arousal state, as reduced brain arousal is related to more head movements, slower response time, and functional connectivity artifacts during resting-state fMRI in young adults (Van Den Berg, 2006; Goodale et al., 2021; Gu et al., 2020). Also, arousal induced by alerting improved performance on an inhibitory task in young adults (Weinbach et al., 2015). Conversely, higher levels of brain arousal in older adults may actually impede the suppression of non-salient stimuli, and thus contribute to poorer inhibitory functioning (Gallant et al., 2020; Lee et al., 2018). The interaction of brain arousal, in-scanner movement, and inhibitory cognitive functioning in older adults has not been explored to our knowledge but could serve as a valuable future direction as arousal state may also underlie the relationship between in-scanner movement and inhibitory performance in older adults.

Subject motion in the scanner is inevitable, especially in older adult populations. Thus, we are left with a perplexing dilemma: how can we preserve the integrity of imaging data via motion correction without excluding participants that may bias our sample? Arguably, the preferable solution would be to proactively limit motion prior to and during scanning, reducing the emphasis on retrospective motion correction post-processing. Strategies such as tactile or visual feedback of head motion (Greene et al., 2018; Krause et al., 2019) and real-time motion monitoring (Dosenbach et al., 2017; Maclaren et al., 2013) have been shown to reduce the deleterious effects of head motion on fMRI data. For example, Dosenbach et al. (2017) developed the Framewise Integrated Real-time MRI Monitoring (FIRMM) software suite that provides head motion analytics in real-time (e.g., framewise displacement values and summary motion statistics) and identifies ideal scan times for each individual to obtain the desired amount of low-movement data. Importantly, this information can be used to facilitate interventions during scanning to encourage participants to remain still or terminate scans early which may reduce costs of time and money. However, this technique may still result in poorer quality or systematic exclusion of data for high-mover older adults, as it relies on implementation of cues or reminders to the participant to reduce movement. This is something an older adult with poor inhibitory functioning may not have the capacity to monitor.

An improved pre-processing pipeline could be another viable option. For example, Satterthwaite et al. (2013) demonstrated that modeling a high number of motion parameters (up to 36) in confound regression models better mitigated changes in signal due to motion in resting-state fMRI, particularly in high movement individuals. Although these models result in a significant drop in degrees of freedom (Lanka and Deshpande, 2019). Satterthwaite et al. (2013) also demonstrated that selectively filtering high frequency signal through band-pass filtering reduced motion artifacts in functional connectivity. Despiking, or the removal of jumps in signal that possibly reflect sudden head movements, has also been explored as a method to reduce motion dependent connectivity without the need for scrubbing (Patel et al., 2014). Additionally, Jo et al. (2013) showed that distance-dependent bias in correlation in resting-state fMRI was exacerbated by including tissue averaged parameters, such as

global signal regression. This suggests that not including global signal as a regressor for a high motion population may be beneficial in resting-state fMRI preprocessing. These somewhat individualized preprocessing approaches may mitigate the need to exclude high movement participants entirely from analyses. However, since there is no gold standard for retrospectively removing motion effects during preprocessing, using these various methods together may detrimentally interact in preprocessing and may require expertise in sophisticated image preprocessing and analysis (Maknojia et al., 2019).

Alternatively, prospective motion correction could be a valuable and effective tool for the older adult population. This technique typically involves the transmission of motion data from external tracking devices to update and adjust the gradient and radio frequency fields in a manner that "follows" the motion in real time (Maclaren et al., 2013). This essentially "allows" participant movement without sacrificing the quality of the data. Morphometry analyses in children and young adults showed higher intraclass correlation between prospective motion correction scans when compared to retrospectively corrected scans and suggest prospective motion correction is most effective in high movement populations (Ai et al., 2021). Preliminary data also show promise when applying prospective motion correction to fMRI data by increasing the signal to noise ratio compared to retrospective motion correction (Zaitsev et al., 2017). A significant advantage to this technique is its accessibility, as most current generation MR scanners come already equipped with prospective motion correction capabilities. Also, if using external tracking devices, it may be applied to most imaging sequences. Nevertheless, the application of this technique has not been validated in an older adult population. Findings from the current study serve as a call to action to validate the efficacy of prospective motion correction in older adult fMRI data, so it may be appropriately implemented without resulting in sampling bias, which is a critical step for research focused on functional brain changes in aging.

4.1. Limitations and future directions

Findings from this study are not without limitations. The current sample consists predominantly of highly-educated, White non-Hispanic individuals, which is not representative of the larger American population, limiting the generalizability of these results. Further, some of the assessments used in this study lack representative normative data for Black, Asian American and Pacific Islander, Indigenous, and Hispanic individuals. Replicating this study in a more diverse, representative sample with appropriate normative reference groups is crucial in broadening the applicability of these findings and exploring the interaction between race/ethnicity, in-scanner movement, and systematic exclusion.

This study only analyzed one parameter of motion: number of invalid scans. This measure is a metric of both framewise displacement and global signal change. While head motion has been demonstrated to explain the most variance in global signal variability (Power et al., 2017), we cannot rule out the influence of physiological variables such as respiration and heart rate on global signal change. Therefore, it would be important for future studies to explore the cognitive correlates of other types of motion correction techniques (i.e., angular and translational or those gathered from external tracking systems) to remove the

potential influence of physiological factors on these relationships and to better understand the strengths and weaknesses across motion correction techniques.

Another limitation includes the use of only the “intermediate” setting on the Artifact Detection Toolbox, which identifies outlier scans as having global signal change of +5 standard deviations and framewise displacement of greater than 0.9 mm. While this setting is what is most commonly used and is recommended by Power et al. (2012), adjusting these settings to reflect more liberal (9SD/2 mm) or conservative (3SD/.5 mm) cut-offs in ART is possible. While conservative motion parameters are recommended for high movement populations, these thresholds come at the cost of eliminating data that may not actually improve the overall quality of the remaining scans and would perpetuate systemic exclusion of high movers (Fair et al., 2013, Lanka and Deshpande, 2019). Currently, there are no studies comparing the impact of varying threshold settings on the relationship between high movement and cognition in older adult populations. Exploring this association is important in generalizing our findings to differing methods of motion thresholds.

Lastly, individuals included in this study were cognitively “normal” and assessed at one point in time. Longitudinal studies could explore the “trait-like” stability of in-scanner motion over time and the cognitive trajectories of high-movers to see if these individuals are at a higher risk for transitioning to mild cognitive impairment or even dementia. Additionally, “cognitively healthy” individuals were recruited for this sample; therefore, the variability in cognitive performance may be restricted. Including individuals who meet criteria for mild cognitive impairment would be important in generalizing these findings, particularly in individuals with amnestic mild cognitive impairment, as this population holds the highest risk for converting to Alzheimer’s disease (Damian et al., 2013).

5. Conclusions

This is the first study to investigate a cognitive profile of in-scanner high-movers in a sample of healthy older adults during a resting-state fMRI sequence. In our sample, poorer performance on tasks in inhibition and cognitive flexibility related to a higher number of invalid scans. This is concerning, as performance in these domains tend to decline in typical aging (Salthouse, 2010) and are necessary for functional independence (Cahn-Weiner et al., 2002; Bell-McGinty et al., 2002; Jefferson et al., 2006). Therefore, these findings suggest that there may be systematic exclusion bias when using the number of invalid scans in fMRI sequences as an exclusion factor in a sample of cognitively healthy aging adults. This highlights the importance of prospective movement reduction and real-time movement monitoring to ensure the integrity of functional MR data while not systemically excluding informative participants.

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Data availability statement

Data are managed under the data sharing agreement established with NIA and the parent R01 clinical trial Data Safety and Monitoring Board in the context of an ongoing Phase III clinical trial (ACT study, R01AG054077). All trial data will be made publicly available 2 years after completion of the parent clinical trial, per NIA and DSMB agreement. Requests for baseline data can be submitted to the ACT Publication and Presentation (P&P) Committee and will require submission of a data use, authorship, and analytic plan for review by the P&P committee (ajwoods@phhp.ufl.edu).

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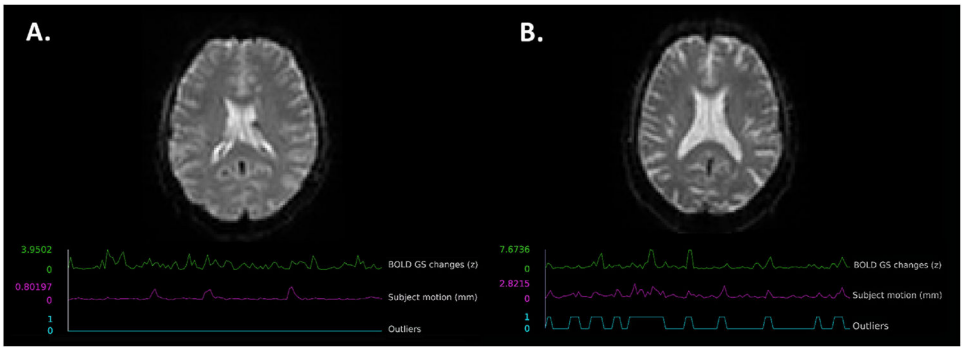

Fig. 1. Artifact rejection toolbox intermediate settings.

Notes: Examples of the global BOLD signal change and subject motion parameters extracted from Artifact Rejection Toolbox for a A) low mover and B) high mover in our sample.

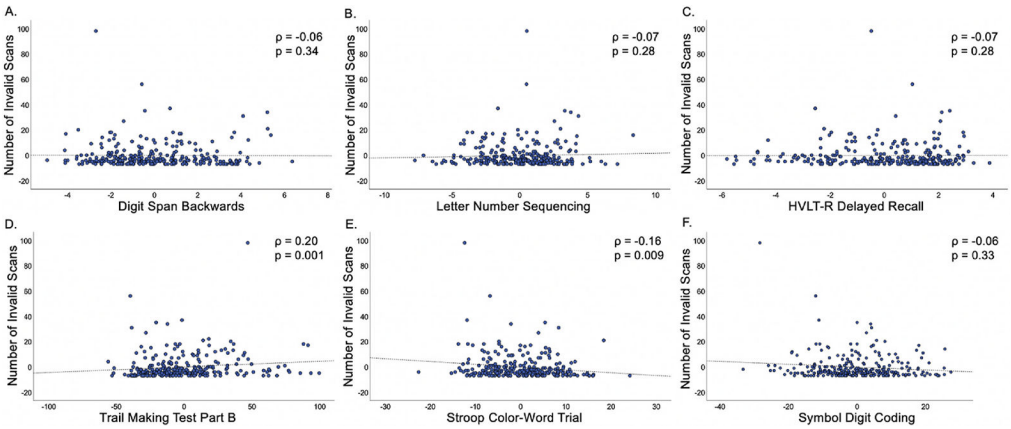

Fig. 2. Spearman rank correlation scatterplots.

Notes: Scatterplots depicting the association between cognitive performance and number of invalid scans for A) Digit Span Backwards, B) Letter Number Sequencing, C) Hopkins Verbal Learning Test - Revised (HVLT-R) Delayed Recall, D) Trail Making Test Part B, E) Stroop Color-Word Trial, and F) Symbol Digit Coding. The X and Y axes represent the unstandardized residuals, partialling out the effects of age and education from the cognitive measure and scanner type from the number of invalid scans. The Trail Making Test Part B metric is the number of seconds taken to complete the task; therefore, greater values reflect worse performance.

Table 1

Sample demographics.

	University of Florida (n = 183)	University of Arizona (n = 99)	Combined (n = 282)
Age M (SD), range	71.53 (5.41), 65-88	71.64 (4.43), 65-84	71.6 (5.10) 65-88
Education M (SD), range	16.20 (2.62), 12-21	16.37 (2.06), 12-20	16.26 (2.44) 12-21
Sex (M:F)	74:109	31:68	105:177

Note. M = mean; SD = standard deviation, M = male, F = female.

Table 2

Raw neuropsychological performance.

Assessment	n	M (SD)	Range
Executive Functioning			
Trail Making Test - B	280	81.40 (30.20)	28.91–189.72
Stroop Color-Word	275	34.90 (7.62)	12–55
Digit Span Backwards	277	8.96 (2.27)	4–16
Letter Number Sequencing	281	19.37 (2.73)	11–27
Processing Speed			
Symbol Digit Coding	277	59.90 (11.52)	27–93
Verbal Memory			
HVLT-R Delay	276	9.46 (2.06)	4–12

Note. M = mean; SD = standard deviation.