Aging-Related Hypometabolism in the Anterior Cingulate Cortex of Cognitively Intact, Amyloid-Negative Seniors at Rest Mediates the Relationship between Age and Executive Function but Not Memory

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Abstract

The anterior cingulate cortex (ACC) shows the most aging-related brain metabolic dysfunction that correlates with decreasing executive processing in otherwise healthy, cognitively intact volunteers. Here, data from ADNI are used to elucidate potential pathophysiological mechanisms involved in cognitive aging, that is, age-related decline in cognitive performance in the absence of known neurodegenerative disease. Amyloid-negative volunteers showed statistically significant mediation of ACC metabolism in the relationship between age and verbal fluency. A nonlinguistic task of executive function, Trails B, showed also negative correlation between performance and age, albeit weaker, but was not significant in the mediation analysis. Recall of story items, minimizing attentional demands compared with learning of word lists, did not correlate with age. ADNI subjects selected for low vascular risks also showed correlation between age and declining ACC metabolism. In the whole-brain amyloid-negative subset, ACC amyloid was not correlated with age. As expected, the metabolism in an arbitrary region such as motor cortex that was not expected to decline with cognitive aging showed no correlation with age or ACC metabolism suggesting regional specificity. These findings motivate the search for the pathophysiology of aging-related ACC dysfunction to prevent, diagnose, and treat the decline in executive function associated with cognitive aging.

Key words: anterior cingulate, cognitive aging, executive function, glucose metabolism, positron emission tomography
**Introduction**

Cognitive aging was considered for many years the inevitable outcome of brain degeneration related to the wear and tear of old age. Many felt cognitive aging and dementia were a continuum. However, neurodegenerative disorders appear in recent years as separate clinical entities. Thus, cognitive aging is an evolving concept that requires definition and differentiation from common disorders such as Alzheimer’s disease (AD) or even other processes yet undefined. Aging and neurodegeneration appear to impact disparate anatomical structures and cognitive operations. Recent developments indicate also phenotypic differences as evidenced by histological and neurochemical biomarkers. The present study considers these aspects in moving forward the neurocognitive characterization of cognitive aging.

Cognitive aging, also termed age-associated cognitive decline, describes the decrease in cognitive performance observed in otherwise healthy, cognitively intact “normal controls” with typical aging free of known neurodegenerative disorders including preclinical AD. These individuals do not have mild cognitive impairment and are clinically rated as 0 on the Clinical Dementia Rating Scale (Morris 1993). Three cardinal cognitive factors that decline during cognitive aging are processing speed, memory, and executive function (Blazer et al. 2015). It remains unclear if unitary or overlapping alterations are associated with these deficits. In contrast, acquired skills, language, and knowledge about facts remain relatively preserved (Salthouse 2010).

Much previous work in cognitive aging may have included individuals that are cognitively intact but with early neurodegenerative pathology. The relationship between cognitive aging and neurodegenerative disease has thus remained unclear. Excluding subjects with preclinical (asymptomatic) Alzheimer’s disease (AD) or very early AD remains difficult even today. AD is the most common dementing illness (WHO 2019), and 30% of elders 85 years and older have dementia (Sköog et al. 1993). Since AD begins 10–20 years before clinical presentation, a substantial fraction of seniors enrolled in studies of cognitive aging may have had an evolving AD neurodegenerative process (Bateman et al. 2012; Jansen et al. 2015).

In recent years, the differences between cognitive aging and AD have become more apparent. For example, human cognitive aging is less associated with dysfunction in the posterior cingulate cortex (PCC), while AD involves the PCC early in its course (Minoshima et al. 1994). Several studies highlight relative preservation of PCC structure and metabolism in the absence of preclinical or early AD (e.g., Buckner et al. 2005; Yanase et al. 2005; Kalpouzos et al. 2009; Shen et al. 2012; Bonte et al. 2017; Ishibashi et al. 2018).

Instead, hypometabolism in cognitive aging affects most prominently the ACC and immediately adjacent regions (Pardo et al. 2007; Vaidya et al. 2007; Ishibashi et al. 2018). Given the dense connectivity between the ACC and PCC, it is likely the PCC may also develop hypometabolism during cognitive aging albeit as a secondary consequence (Wang et al. 2012). The ACC is a central structure involved in human attention and is associated with many executive functions such as selective attention, resolution of conflict, multitasking, semantic generation and fluency, and adaptation to changing contexts (Petersen and Posner 2012). The aging-related decline in ACC glucose metabolism correlates with the decline in executive function based on 1) scores from a cognitive acuity screen as well as 2) a commonly used test of executive function such as verbal category semantic fluency (Pardo et al. 2007). Of note, verbal fluency/semantic generation was among the earliest cognitive activation paradigms shown to activate the ACC (Posner et al. 1988). Impaired cognitive processing not only impacts daily life in those free of neurodegenerative diseases but also disrupts cognitive reserve that can ameliorate the sequelae of early neurodegeneration through ACC processing. In other words, individuals with preclinical AD or MCI are less able to deploy cognitive reserve through ACC attentional mechanisms prompting clinical presentation earlier than those with greater cognitive reserve. Patients with incipient AD who have exposures including high educational and occupational attainment have far greater neuropathology on clinical presentation and more rapid decline (Stern 2012).

The current study aims to examine the relationships between age, resting ACC metabolism, executive function, and memory in normal controls especially without whole-brain amyloid positivity. The study was motivated by the need to define pathophysiological mechanisms of aging-related phenomena within the ACC—a prerequisite to develop prevention strategies and treatments for the cognitive decline that occurs in aging unassociated by preclinical AD or early AD.

**Materials and Methods**

**Participants**

All participants provided written informed consent as approved by the Institutional Review Boards (IRB) of the respective institutions participating in ADNI. Data from 231 participants aged 56–93 years (108 males, 123 females, mean age 74 years, SD 7) assessed as cognitively normal were obtained from LONI (subject identification numbers are provided as Supplementary material in .csv file). Participants had a score between 24 and 30 on the Mini-Mental State Exam (MMSE), had a Clinical Dementia Rating (CDR) of 0; and were not MCI, demented, or depressed (see ADNI for further diagnostic criteria). These participants had completed 6 or more years of education and were fluent in either English or Spanish.

Participants’ ages and scores on category verbal fluency, Trails B, and Logical Memory were obtained from ADNI and were appropriate matched to the mean glucose uptake in an ACC region of interest (ROI). The ACC ROI and verbal fluency task were identical to those used in a previous study of cognitive aging (Pardo et al. 2007). Fluency was scored using the “animal” category (i.e., name as many animals as possible in 1 min) and served as a measure of executive performance. Memory for story items used Logical Memory I (immediate recall) and II (delayed recall). A subset of the 231 subjects was selected based on having amyloid below the threshold for positivity (see below: Imaging). This subset consisted of 155 participants aged 59–93 years (78 males, 77 females, mean age 74 years, SD 6.6). This subset was also filtered to include only subjects with normal cognition for at least 5 years beyond the baseline assessment (N = 9); ages 75–86 years.

The risk of vascular disease was indexed by the Hachinski Ischemia Score, an extensively used measure of vascular/cognitive dysfunction in community dwelling elders (Hachinski et al. 1975). Another subset of the original 231 subjects was filtered to have Hachinski Ischemia Score = 0 (N = 103) or Score = 1–3 (N = 103).

**Imaging**

FDG PET scans in the resting state from the Alzheimer’s Disease Neuroimaging Initiative (ADNI@LONI.USC.EDU) were downloaded. These were stereotactically normalized to standard...
and fluency scores. All pathways were tested simultaneously. Analyses and computations were performed using R, version 3.5.1 (http://www.R-project.org). The mediating or regression effect was considered significant (i.e., different from 0) at the corresponding confidence level if the upper and lower bounds of the confidence interval had the same sign.

Second, the ACC’s role in executive function versus memory and the potential confounding of linguistic processing in fluency were examined. An exploratory analysis tested the relationship between the measures above versus Logical Memory I & II as well as Trails B. Cognitively intact older subjects who were either whole-brain negative for amyloid (N = 155) or not (N = 235) were analyzed separately.

Results

Correlations between Age, Resting ACC Metabolism, and Fluency in Cognitively Intact Seniors (Normal Controls)

The normal controls regardless of amyloid status were examined first. For comparison, Figure 1A shows the voxel-wise correlation from the dataset reported in Pardo et al. 2007 (N = 46; ages 18–90 years.). Figure 1B displays a similar analysis for ADNI data (N = 210; 56–90 years.). Likewise, Figure 1C,D show similar analyses on the subsets with Hachinski Ischemia Score of 0 (N = 103, 56–90 years.) or 1–3 (N = 103; 63–89 years.). Table 1 quantitates the peak FDG correlations with age in Figure 1 as well as the peak correlations of age with amyloid deposition.

ACC Metabolism Mediates the Relationship between Age and Fluency in Normal Controls Negative for Whole-Brain Amyloid

As discussed previously, contamination of cognitively normal subjects by individuals with preclinical or very early MCI can confound the study of cognitive aging. In the current state of knowledge, it is admittedly not possible to completely rule out preclinical AD. To minimize this possibility, only amyloid negative, cognitively normal subjects from ADNI (i.e., normal controls) were examined (N = 155). ADNI’s designation of amyloid positivity was SUVR > 1.1 derived from AD-critical ROIs.

A correlation matrix describes the relationships between the variables of interest for exploratory analysis (Table 2). Significant correlations along with their respective explained variances are age versus ACC metabolism ($R^2 = 26\%$); ACC metabolism versus fluency (9%); and age versus fluency (7%).

A mediation model is shown in Figure 2 where ACC metabolism mediates the relationship between age and fluency. The nonparametric bootstrap tests the significance of the mediation model (i.e., ab) as displayed in Table 3. The total effect (c; total effect; $−0.267$) equals the average direct effect (c; ADE; $−0.154$) plus the average causal mediated effect (ab; ACME; $−0.113$). A measure of the effect size considers both c and $P_M$, the ratio of the indirect effect to the total effect (i.e., $P_M = ab/c$). Here, $P_M = 0.56$, a large proportion tempered by a modest to moderate total effect ($−0.026$).

Relative Roles of Executive Function versus Memory in Aging-Related ACC Dysfunction in Normal Controls with Negative Whole-Brain Amyloid

The performance in a nonlinguistic task of executive function, Trails B, showed a modest but significant negative correlation with age but was not significantly correlated with ACC
Figure 1. Whole-brain voxel-wise correlation between age and FDG uptake. Data from the following: (A) Pardo et al. 2007; (B) ADNI; (C) ADNI with Hachinski Ischemia Score = 0; (D) ADNI with Hachinski Ischemia Score = 1–3. The correlations are much greater in (A) because the age range was broad (18–90 years), whereas ADNI’s range began at 56 years. Note the ADNI Hachinski Ischemia Score = 0 voxel-wise correlations were greater than those in ADNI Hachinski Ischemia Score = 1–3. The low-level positive correlations in the cerebellum (A) have been reported previously as related to whole-brain normalization (Willis et al. 2002). Color scale displays pixelwise correlation coefficients for panels (A–D) and was quantitated in Table 1.

Table 1. ACC voxel-wise correlations between age and radioligand uptake

| Ligand                  | N  | R     | P      |
|-------------------------|----|-------|--------|
| 18F-FDG                 | 210| −0.53 | 1.1 (10)−16 |
| 18F-FDG Hachinski 0     | 103| −0.61 | 5.3 (10)−12 |
| 18F-florbetapir         | 210| +0.06 | 0.36   |
| 18F-florbetapir (Hachinski 0) | 103| +0.10 | 0.33   |

Table 2. Correlations between age, ACC metabolism, fluency scores, and metabolism in the right motor cortex

| Variable                  | Age  | ACC metabolism | Fluency | R motor cortex metabolism |
|---------------------------|------|----------------|---------|----------------------------|
| Age                       | 1.00 | −0.51**        | −0.27** | −0.08                      |
| ACC metabolism            |      | 1.00           | 0.30**  | 0.13                       |
| Fluency                   |      |                | 1.00    | −0.001                     |
| R motor cortex metabolism |      |                |         | 1.00                       |

*P ≤ 0.05. **P ≤ 0.01.

Table 3. Bootstrap shows significant mediation effects of ACC metabolism on age and fluency relationship (N = 155)

|                  | Estimate   | 95% CI       | P-value |
|------------------|------------|--------------|---------|
| ACME             | −0.1129    | [−0.2193, −0.02] | 0.0204* |
| ADE              | −0.1541    | [−0.3218, 0.02]  | 0.0888  |
| Total effect TE  | −0.2570    | [−0.3977, −0.13] | <4 (10)−4** |
| Prop. mediateda  | 0.4229     | [0.0599, 1.16]  | 0.0208* |

Simulations = 5000.
ACME = Average Causal Mediation Effects (ab).
ADE = Average Direct Effects (c').
c (total effect, TE) = ab + c'.
This is not a true ratio as it is unbounded (i.e., >1). See Preacher and Kelley (2011).
*P ≤ 0.05.
**P ≤ 0.01.
metabolism except at a trend level for the entire sample (Table 4; \(N = 235; P = 0.08\), Supplementary Table 1). The mediation analysis was neither significant for those who were negative for amyloid nor for the entire sample (Supplementary Table 2). In contrast, neither Logical Memory I (immediate) nor Logical Memory II (delayed) showed a correlation with age in these cognitively intact, amyloid-negative seniors (Table 4). Similar results about memory surfaced for the entire group (cognitively intact; amyloid positive or negative) as well (Supplementary Table 3).

**ACC Amyloid versus Age in Normal Controls with Negative Whole-Brain Amyloid**

Amyloid is known well to increase with age and to cause neuronal dysfunction and hypometabolism suggesting potentially a causal influence on age-related ACC hypometabolism. There was no correlation between age and ACC amyloid in these cognitively intact normal controls, \(\geq 56\) years old negative for whole-brain amyloid. In the subset of subjects who were both amyloid negative and cognitively intact for at least 5 years...
Age and ACC Metabolism in a Control Region (Right Primary Motor Cortex)

To determine whether the relationship between age and ACC metabolism occurs globally, the motor cortex was selected as a control region since it is not known to process executive functions and is minimally affected by amyloid in AD. Table 2 demonstrates no correlation between metabolism within the right motor cortex (right motor cortex) and age ($r = -0.08, P = 0.32$) or fluency ($r = -0.001, P = 0.99$). In contrast to the results seen for ACC metabolism as a mediator between age and fluency, age did not predict metabolism in the right motor cortex. A bootstrap estimation did not show a decrease in the effect of age on fluency when controlling for metabolism in the right motor cortex (not shown).

Discussion

These results indicate for the first time that ACC metabolism mediates the relationship between aging and executive function in normal controls negative for whole-brain amyloid thereby imputing some unknown pathophysiology in aging-related cognitive decline. In contrast and despite decline in memory is considered a sine qua non for aging, logical memory was not correlated with age. As expected, given the primary motor cortex does not play a major role in executive functions but rather in the control of motion sequences (i.e., force, speed, direction), no such relationships surfaced when examining the metabolism of the right motor cortex indicating at least some regional specificity to the effects of age on metabolism.

ACC Metabolism is a Mediator of the Relationship between Age and Fluency in Healthy, Cognitively Intact, Amyloid-Negative, Older Adults

Previous results that spanned a broad range of ages (18–90 years) with a more limited sample size of 46 subjects reported a decline in metabolism within an identical ACC ROI that correlated with declining executive function as measured by the same animal fluency task (Pardo et al. 2007). The decline in ACC flow or metabolism with age had been reported previously by several groups; however, the relationship of ACC metabolism to executive function in cognitive aging had not been noted previously. The amyloid-negative subset of the ADNI dataset used here has a much larger sample size ($N = 155$) but narrower age range (56–92 years) and does not include young adulthood. However, ADNI data enabled not only replication of previous findings on a different sample of subjects but also enough power to show that ACC metabolism was statistically a mediator of the relationship between age and fluency even in older cognitively normal adults free of amyloid. The significance of mediation over simple correlation is the former supports the idea that ACC metabolic dysfunction plays a crucial role in age-associated cognitive decline. ACC hypometabolism was not related to vascular risk factors; also, ACC amyloid did not correlate with age. As such, ACC hypometabolism could serve as a potential biomarker for cognitive aging in the absence of neurodegeneration.

Limitations

ACC ROI Definition and Multiple Comparisons

This research was motivated specifically by prior reports of ACC metabolic dysfunction in cognitive aging (see above and others sic passim). This region showed high negative correlations of metabolism with age extending throughout a broad region in the ACC and medial prefrontal cortex making the precise placement of the ROI less an issue. Figure 1A displays the high magnitude and broad extent of age-related hypometabolism making the precise placement of the ROI unnecessary. With an eye to test for replication, the ACC ROI was identical to that used in a previous report (Pardo et al. 2007). ACC subregions are densely interconnected structurally themselves. To what extent these regions represent primary or secondary effects of aging remains for further study. An exhaustive search for other areas mediating executive function in the ADNI dataset that might show a high correlation with age was not done. In part, problems in ROI definition, particularly with newer parcellation schemes, and concerns about multiple comparisons dissuaded such an approach.

Recently, there has been increasing interest in refining the localization of the ACC and the midcingulate cortex (MCC) with associated functions (van Heukelum et al. 2020). The area of ACC hypoactivity seen here clearly spans parts of both regions. At this time, the resolution of PET precludes more precise specification of the parcels. Seed analysis of static FDG PET functional connectivity of ADNI data suggests that these areas are densely interconnected themselves precluding identification of primary versus secondary sources of dysfunction (A. Gidwani and J.V. Pardo, unpublished observations).

Preclinical AD

Another issue is concern about possible inclusion of preclinical AD in the cognitively intact elderly sample. Exclusion of preclinical AD remains problematic even today. The exclusion of SUVR—positive subjects strengthens confidence that the subjects studied did not have preclinical AD. However, cross-sectional neuropathological studies suggest that a significant number of demented individuals with extensive tau pathology have minimal fibrillar plaques (Braak and Del Tredici 2015). Also, amyloid PET cannot detect diffuse plaques; so, this remains a possibility for those with negative amyloid scans. Furthermore, even normal controls negative for whole-brain amyloid can show increasing deposits of amyloid and tau with changes in cognitive performance, task activation, and medial temporal atrophy (Marks et al. 2017).

Atrophy and Partial Volume Correction

The PET data did not undergo partial volume correction (PVC). ACC hypometabolism could reflect focal atrophy without a change in gray matter metabolism. However, PVC can introduce noise especially when volume changes are small. Vaidya et al. (2007) reported that even with PVC, the age-related decline in ACC blood flow (correlated with metabolism) could not be totally accounted for by atrophy. The correlations between flow and age were much larger than correlations between age and gray matter volume, and some regions (e.g., left dorsal ACC) showed strong correlation with age without a change in gray matter volume.

Whether the ACC shows any atrophy with age remains controversial. Two large cross-sectional studies using scans at high resolution found thickening of the ACC gray matter with aging (Salat et al. 2004; Fjell et al. 2009). A longitudinal study also...
with a large sample size and high-resolution structural scans did not find ACC thickening with age over a 3-year period but neither did it show gross atrophy (Fjell et al. 2014). This apparent discrepancy could result from selection bias: higher functioning normal, cognitively intact, seniors may be recruited selectively in cross-sectional studies. However, another longitudinal study of cognitively intact elders did not show significant ACC volume changes over 4 years but did find significant decreases in the ACC FDG uptake even with correction for partial volume effects (Castellano et al. 2019).

There is also evidence ACC thickness may vary by state or trait. Aged individuals who have memory performance akin to those who are much younger (i.e., “SuperAgers”) show a thickened ACC (Rogalski et al. 2013; Gefen et al. 2015). Education serves often as a proxy for cognitive reserve. In amyloid-negative healthy elders, the years of education correlate positively with ACC volume, ACC metabolism, and ACC functional connectivity with the hippocampus and PCC (Arenaza-Urquijo et al. 2013; Barttes-Faz et al. 2019). Furthermore, sedentary elders show increased ACC volume in a between-group comparison following an intervention with aerobic versus stretching exercises (Colcombe et al. 2006).

Relationship to Other Anatomical Regions and Cognitive Tests

As noted above, this project aimed specifically to expand findings in cognitive aging in the ACC based on prior works (Pardo et al. 2007; Vaidya et al. 2007; Ishibashi et al. 2018). No attempt was made to exhaustively evaluate other regions (e.g., based on FreeSurfer or Connectome Workbench). In part, the large extent of aging-related hypometabolism even after accounting for Gaussian blurring indicated the observed changes were not restricted to a specific parcel. Similarly, the focus was on executive function given the ACC’s association with declining verbal fluency and aging. Therefore, other regions may also mediate verbal fluency.

Another frequent measure of executive function is Trails B and does not depend on language. Aging was also associated with declining performance in Trails B. However, the mediation analysis did not reach significance as the correlations were more modest. This finding addresses the potential confound that the linguistic component of verbal fluency was responsible for aging-related decline.

Episodic memory is often considered the sine qua non of cognitive aging. Many have hypothesized that a significant decline in memory in aging is mediated by executive dysfunction in older adults (Isingrini and Taconnat 2008; McCabe et al. 2010). Further, the frequent presence of preclinical AD in the older sample would highlight mnemonic deficits.

Episodic memory is often tested using lists of words or recall of items from a story presented at an earlier time. Recall of story items takes advantage of semantic processes, while recall of word lists requires self-generation of mnemonic strategies. Memory of word lists taxes the executive system more than does story recall. For example, patients with frontal lesions and those with executive dysfunction do worse on recall of word lists than on recall of items from paragraphs presented previously (Kopelman and Stanhope 1998; Brooks et al. 2006). In contrast, memory for semantically-related information depends more on medial temporal processes (Tremont et al. 2000; Lezak et al. 2004). Therefore, when attempting to differentiate the ACC’s role in executive versus mnemonic processes, the Logical Memory test is preferred.

However, given that most cognitive tests show intercorrelations in performance measures (Table 4), it is difficult to dissect the contribution of specific structures to cognitive measures. In other words, no test of executive function or memory is “process pure.” It is unclear whether the relationship between age and memory versus executive function is dissociably associated or more mechanistically related. These are critical caveats in interpreting the relative aging-related performance differences in executive versus mnemonic functions.

Correlation in Cross-Sectional Studies

Correlational and cross-sectional studies can confound interpretation. As in most research using convenience samples, the ADNI database is neither random nor without bias; it is also susceptible to cohort effects (Whitwell et al. 2012). Different pathophysiology may participate in ACC dysfunction during different time intervals across the lifespan. For example, most loss in aerobic glycolysis occurs before age 55 years (Goyal et al. 2017). In contrast, decreased brain glucose uptake (i.e., glucose uptake constant) may occur later in life when peripheral insulin resistance increases (Castellano et al. 2019).

Effect Size of ACC Mediation

How much does ACC metabolism mediate the relationship between age and executive function? When a mediator produces a nonsignificant direct effect (i.e., c), the mediator is often considered a total mediator of the relationship between the independent variable and outcome. However, a better measure is the reporting of effect size, which in the case of mediation studies remains in debate. The criteria for the ideal characteristics of effect size for mediation analyses have been previously outlined (Preacher and Kelley 2011). All measures proposed appear to have some limitation. Here, recent recommendations were followed (Wen and Fan 2015). $P_M$ (ratio of indirect effect to total effect; 0.56) was large suggesting robust mediation. However, this ratio needs qualification since the total effect was not very large ($c = -0.267$). Given both $P_M$ and $c$, the combined measures communicate effect size well.

Association versus Causality

Association does not prove causality. Regional ACC effects could come from extrinsic regions; that is, ACC dysfunction is an effect rather than a cause. However, no other brain region showed greater decline in magnitude or greater areal extension of the correlation between metabolism and age. Nevertheless, the results highlight the ACC as a critical region to look for pathophysiology which will require an animal model.

Conclusion

In summary, ACC metabolism mediates the relationship between age and executive function in cognitively intact, amyloid-negative elders. This relationship does not occur everywhere throughout the brain consistent with the known specialization of the ACC for executive functions. In contrast, episodic memory as tested here in the amyloid negative sample did not decline with age. Tentatively, neither vascular effects nor amyloid appeared causal. These findings motivate additional research on aging-related ACC pathophysiology and the need for animal models of cognitive aging.

Notes

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