Title: A new role of hippocampus during logical reasoning and belief bias in aging

Running title: Aging, belief bias, and hippocampus

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Abstract

Reasoning requires initial encoding of the semantic association between premises or assumptions, retrieval of these semantic associations from memory, and recombination of information to draw a logical conclusion. Currently-held beliefs can interfere with the content of the assumptions if not congruent and inhibited. This study aimed to investigate the role of the hippocampus and hippocampal networks during logical reasoning tasks in which the congruence between currently-held beliefs and assumptions varies. Participants of younger and older age completed a series of syllogistic reasoning tasks in which two premises and one conclusion were presented and they were required to decide if the conclusion logically followed the premises. The belief load of premises was manipulated to be either congruent or incongruent with currently-held beliefs. Our whole-brain results showed that older adults recruited the hippocampus during the premise integration stage more than their younger counterparts. Functional connectivity using a hippocampal seed revealed that older, but not younger, adults recruited a hippocampal network that included anterior cingulate and inferior frontal regions when premises were believable. Importantly, this network contributed to better performance in believable inferences, only in older adults group. Further analyses suggested that, in older adults group, the integrity of the left cingulum bundle was associated with the higher correct rejection of believable premises more than unbelievable ones. Using multimodal imaging, this study highlights the importance of the hippocampus during premise integration and supports the compensatory role of the hippocampal network during a logical reasoning task among older adults.

Keywords: Hippocampus, aging, logical reasoning, white matter tract, cingulum, functional connectivity, multivariate analysis,

Introduction

Logical reasoning, drawing a reasonable conclusion from related facts and assumptions, plays a central role in personal, complex political and societal decisions. Beliefs and prior knowledge, however, may contradict the given information and if they overshadow logic, unwarranted conclusions may be drawn; a phenomenon known as belief bias (De Neys, 2012; Evans et al., 1983). In this situation, inhibition of currently-held beliefs is required to reach a logical conclusion, mainly engaging the prefrontal areas (Goel et al., 2000). While mounting evidence supports the role of frontal cortices in belief bias when currently-held beliefs contradict the given assumptions (for a review see Prado et al., 2010), the role of subcortical regions, such as the hippocampus, has not been fully understood. To date, only few studies have reported the hippocampal activity during various reasoning tasks. For instance, Goel et al. (2004) found that the hippocampus is involved when a task involves reasoning about familiar spatial environment. Zeithamova and colleagues (2012) have also examined the role of hippocampus in retrieving individual memories to answer a novel question in inferential reasoning. Another study reported that hippocampus was active during a transitive inference, where consideration of multiple relations is required to reach a logical conclusion (Wendelken et al., 2010). While these studies have highlighted the importance of hippocampus in reasoning tasks, the exact form of hippocampal engagement and its connection with the prefrontal areas in syllogistic reasoning has not been thoroughly investigated. Given the hippocampus involvement in detecting conflicts between the current situation and prior experience (Kumaran et al., 2007) and retrieval of semantic knowledge, it is reasonable to assume its role in syllogistic reasoning. This is particularly important during premise integration stage where currently-held beliefs are retrieved from memory and compared with given assumptions. Thus, we suggest that the hippocampus - which is known to be associated with declarative memory - is essential for a flexible and valid reasoning decision. Therefore, activity of the hippocampus is expected to appropriately construct, manipulate, and update information to respond to the task at hand.

Age-related changes in the structure and function of the hippocampal-cortical networks

Existing literature indicates a complex pattern of activities in the aging brain during cognitive tasks. One view posits an over-recruitment of alternate brain circuits which is associated with maintained behavioral performance among older adults. In this view, increased

activity of the prefrontal and other areas is interpreted as compensatory (Davis et al., 2008). Contrary to the over-recruitment view, some studies found no difference between two age groups in performance or brain activity, supporting the brain maintenance hypothesis (for a review see Nyberg et al., 2012) and others found age-related decline (Nyberg et al., 2010; Persson et al., 2006). More specific to underlying brain networks in aging, there is considerable evidence that the behaviors dependent on the hippocampus undergo substantial changes in aging (Samson et al., 2013). Pattern of hippocampal connections with cortical areas (whether directly or indirectly) is also altered (For a detailed overview see Eichenbaum, 2017) which has been linked to changes in cognitive functions in late adulthood (Carr et al., 2017; Fjell et al., 2016; Salami et al., 2014).

Despite reports of age-related hippocampus-prefrontal cortex (PFC) alterations, little is known about changes in this connectivity during a complex cognitive task such as logical reasoning. To date, only few studies have investigated age-related differences in belief bias and reasoning. De Neys and colleagues (2009) reported a reasoning performance decrease among older adults when belief and logic were in conflict, but not when they were congruent. In another study, Tsujii and colleagues (2010) replicated these findings and reported that older adults, unlike younger counterparts, recruited the bilateral inferior frontal gyrus when belief and logic were in conflict. While these studies highlight the decline in reasoning performance among older adults, our understanding of neural networks underpinning a logical reasoning task in late adulthood is still incomplete. Therefore, the primary aim of this study was to investigate age-related differences in functional engagement of the hippocampus and hippocampal network during a syllogistic reasoning task in which premises were either congruent or incongruent with prior knowledge. For this purpose, we used a performance measure to quantify the ability of participants to successfully inhibit the incongruence between the belief load of the statements and their currently-held belief and make correct, logically sound, decisions.

Given that lower white matter integrity has shown to contribute to age-related cognitive decline (Madden et al., 2009), our secondary aim was to investigate whether the structural integrity of the hippocampus-prefrontal pathway is associated with reasoning performance in aging. There is convincing evidence for age-related changes in the white matter microstructure that affect cognitive functions (Charlton et al., 2006; Choi et al., 2005; Fjell et al., 2010; Goh et al., 2009; Tuch et al., 2005). Specifically, integrity of white matter tracts, such as uncinate fasciculus and cingulum bundle, are integral for inhibitory control and executive functioning

tasks (Catani, 2010; Grieve et al., 2007; Li et al., 2018). Changes in these tracts have been associated with altered performance during executive function and inhibitory control in late adulthood (Davis et al., 2009; Hasan et al., 2009; Li et al., 2018; Vogt et al., 1992), thus, demonstrating a significant covariance between their structural integrity and performance during a reasoning task.

Current study

The aim of this study was twofold: first, to investigate age-related differences in hippocampal networks during a logical reasoning task, and second, to examine the relationship between the structural integrity of hippocampal tracts and logical reasoning performance across both age groups. Younger and older participants performed a syllogistic reasoning task in which they identified if a conclusion logically followed two given premises where the believability of the premises was manipulated. Premises were either believable (congruent with currently-held belief: e.g. all parrots are birds), unbelievable (incongruent with currently-held beliefs: e.g. all lizards are mammals) or neutral (no believability load: all sothods are birds – where sothods is a pseudo-word). Three main analyses were conducted. First, using whole-brain analysis and using a multivariate method, we examined whether there are any age-related differences in brain networks as a function of believability content of the syllogisms. Given the differences in analytical methods and lack of age group comparison in previous literature, there is still a need to discern a neural correlate of logical reasoning among older adults. Second, using brain-behavior connectivity analysis, we explored whether activation of the hippocampal network during second premise differed between two age groups. Third, using structure-function analysis, we investigated whether the structural integrity of tracts involving hippocampus, such as cingulum bundle and the uncinate fasciculus, was correlated with logical reasoning performance. As we aimed to characterize the ability to inhibit currently-held belief during a reasoning task, the "performance" was defined by the number of correctly accepted syllogisms with unbelievable premise and correctly rejected syllogisms with believable premise.

Hypotheses

In whole-brain analysis, we anticipated stronger hippocampal activity during premise integration more for believable condition because of a stronger semantic association between currently-held beliefs and given assumptions when the content is believable. As for aging

prediction, given that there is still lack of knowledge on age-related functional networks underlying logical reasoning and belief bias, our expectations are three-fold: a) An age-related enhanced activity of the hippocampal-PFC network – and its positive association with the task performance – supports the pattern of regional over-recruitment or compensatory mechanism; b) An age-related decline in hippocampal-PFC network activity suggests a link with age-related decline in gray matter, white matter and neurochemical functioning during cognitive tasks; and c) A lack of age-related difference in the hippocampal-PFC network activity with equal performance between two age groups, supporting the notion of brain maintenance model.

Lastly, converging evidence suggests a link between white matter microstructure underlying functional compensatory network and behavioral performance in aging, clarifying the link between structural, functional, and behavioral performance during a higher cognitive task (Davis et al., 2009; Fjell et al., 2016; Nordahl et al., 2006). Thus, our predictions on the structural changes of the hippocampus-PFC pathways are three-fold and aligned with our functional connectivity predictions stated above: (a) If the hippocampus-PFC network is involved, then we anticipated that the structural integrity of tracts involving the hippocampus and PFC (uncinate fasciculus and cingulum bundle) contribute to the behavioral performance. That is, older adults who have higher integrity in these tracts would perform better during a logical reasoning task; (b) If there is an age-related decline in the functional recruitment of the hippocampus-PFC network, lower structural integrity of these white matter tracts and lower reasoning performance among older adults comparing to the younger is expected; and (c) If there is no age-related difference in the functional network of the hippocampus-PFC as stated above, fewer losses in structural integrity of the white matter tracts and thus, lesser decline in behavioral performance among older adults is expected.

Material & Methods

Participants

Thirty-one healthy younger and thirty-two healthy older adults participated in this study. Due to extensive head movement and brain signal loss, two older and two younger adults were excluded from the analysis due, leaving 29 younger adults (aged 18-26 years; M = 21.13, SD = 2.72; 15 females) and 30 older adults (aged 61-78 years; M = 70.34, SD = 4.27; 15 females).

Younger adults were recruited from The University of Queensland and were reimbursed either with course credits or AUD$15 per hour. Older adults were volunteers from the community recruited through flyers on notice boards in local bowls and Rotary Clubs, University of Third Age, libraries, churches, and The University of Queensland's Aging Mind Initiative. Older adults were reimbursed AUD$20 per hour. Participants were screened for MRI compatibility, mood disorder (depression and anxiety), claustrophobia, significant neurological and psychiatric disorders before enrolment in the study. All participants were English speakers, right-handed, with normal or corrected-to-normal vision using MRI compatible glasses. Older adults underwent additional screening to rule out cognitive decline on the Mini Mental State Examination (Folstein et al., 1975), a widely used dementia screen; all older adults scored above the recommended cut-off of 24 (M = 29.34, SD = 0.82). All participants took part in two separate test sessions, the first involving MRI scanning and the second involving behavioral and neuropsychological assessments. All participants were provided with written consent forms and were debriefed upon the completion of the second session. The experiment was approved by the Bellberry Human Research Ethics Committee.

Task materials

Logical arguments in this study were in the form of standard syllogisms and included three statements: two premises and one conclusion. The subject and the predicate of a premise was formed by arbitrary sets (e.g., dogs, mammals, furniture). The two premises had exactly one set in *common* that may appear in either the subject or the predicate in either of the premises. Hence, the two premises involved exactly three sets, two of which are uniquely used in each premise and one which is used in both. The conclusion of a syllogism provides a statement about the sets that appear uniquely in premises. A conclusion "follows" from the premises if the premises provide conclusive evidence to support it. Otherwise, the conclusion "does not follow" from the premises, either because the conclusion is wrong given the premises, or is not completely supported by the premises.

Conclusions and premises were either believable or unbelievable in terms of the belief load. For example, "all dogs are animals" is a believable statement while "all birds are mammals" is an unbelievable statement. In addition, control premises with a neutral load comprising a meaningless pseudo-word were used (e.g. "all parrots are nickhomes", where

“nickhomes” is a neutral word without any belief load). Pseudo-words were only used in the premises so that they were a shared set between the premises. Hence, the first premise was always believable while the second premise’s believability was manipulated (believable, unbelievable, or neutral) while the conclusion was either believable or unbelievable. The following are two examples of syllogisms with a believable premise / unbelievable conclusion and an unbelievable premise / believable conclusion, respectively:

All pines are trees; No pines are willows; Therefore, all trees are willows (believable premise/unbelievable conclusion; logically invalid)

All lories are parrots; No parrots are animals; Therefore, some animals are not lories (unbelievable premise/believable conclusion; logically valid)

A total of 96 syllogisms was generated using an in-house algorithm. Six conditions included in the task: 1. believable premise/believable conclusion, 2. believable premise/unbelievable conclusion, 3. unbelievable premise/believable conclusion, 4. unbelievable premise/unbelievable conclusion, 5. neutral premise/believable conclusion, 6. neutral premise/unbelievable conclusion (see Supplementary Material for access to all of the syllogisms used in the study and details on how the syllogisms were constructed).

Experimental design

Prior to the scan, participants were instructed about the task and procedure of the scanning session. A practice run was administered until they were familiar with the timing and instruction of the task. The imaging session included two components: two structural MRI scans (T1-weighted scans and Diffusion Weighted Imaging (DWI) scans) and the logical reasoning task with functional MRI (fMRI) and lasted for 45 minutes in total. During the logical reasoning task, participants were asked to determine if the conclusion statement logically followed from the two premises using two keys on an MRI-compatible response box. The first premise was presented for 2 seconds followed by a second premise for 4 seconds. After the second premise, the conclusion statement was presented for 12 seconds (Figure 1). All statements (premises and conclusion) remained on the screen until the end of the presentation of the conclusion to reduce the working memory load. A jittered fixation cross was presented after the conclusion with four-time intervals: 0.5 seconds (24 trials), 1 second (24 trials), 1.5 seconds (24 trials), and 2 seconds

(24 trails). The task consisted of 6 runs, each run lasting for 5.16 minutes with three runs of the task presented before and three after the structural scan.

[Insert Figure 1 about here]

Background measures

In addition to the imaging session, all participants completed a number of tasks to assess emotional well-being as measured by the Depression, Anxiety, Stress Scale (DASS-21; Lovibond & Lovibond, 1995[44]), executive functioning as measured by the Stroop task and the Trail Making Test (Reitan et al., 1986), and intelligence as measured by the National Adult Reading Test (Nelson, 1982). Descriptive and inferential statistics of background measures are reported in Table 1.

[Insert Table 1 about here]

Image acquisition

Functional images were acquired at the Centre for Advanced Imaging using a 3T Siemens scanner with a 32-channel head coil. The functional images were obtained using a whole-head T2*-weighted multiband sequence (473 interleaved slices, repetition time (TR) = 655ms, echo time (TE) = 30ms, voxel size = 2.5mm^3, field of view (FOV) = 190mm, flip angle = 60º, multi-band acceleration factor = 4). High-resolution T1-weighted images were acquired with an MP2RAGE sequence (176 slices with 1mm thickness, TR = 4000ms, TE = 2.89ms, voxel size = 1mm^3, TI = 700ms, FOV = 256mm). Participants were provided with cushions and earplugs around their head inside the head coil to minimize the noise and head movement. Participants observed the tasks on a computer screen through a mirror mounted on top of the head coil.

fMRI Preprocessing

For functional analysis, T2*-weighted images were preprocessed with Statistical Parametric Mapping Software (SPM12; http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB 2015b (Mathworks Inc., MA). Following the realignment to a mean image for head-motion correction, images were segmented into gray and white matter. Then, images were spatially normalized into a standard stereotaxic space with a voxel size of 2 mm^3, using the Montreal Neurological Institute (MNI) template, and then spatially smoothed with a 6 mm^3

Gaussian Kernel. None of the participants included in the analyses had head movement above1mm.

fMRI analyses

The imaging data were analyzed using a multivariate analytical technique Partial Least Squares analysis (PLS; McIntosh et al. (1996)) as implemented in PLS software running on MATLAB 2012b (The MathWorks Inc., MA). For a detailed tutorial and review of PLS, see Krishnan et al. (2011). PLS analysis uses singular value decomposition (SVD) of a single matrix that contains all data from all participants to find a set of orthogonal latent variables, which represent a linear combination of the original variables. PLS decomposes all images into a set of patterns that capture the greatest amount of covariance in the data, without making assumptions about conditions or imposing contrasts. Using PLS enables us to differentiate contribution of different brain regions in relation to the task demands, activation of a functional seed, behavioral or anatomical covariates. Each latent variable delineates cohesive patterns of brain activity related to experimental conditions. Usually, the first latent variable accounts for the largest covariance of the data and progressively smaller amounts of covariance are attributed to subsequent latent variables. The brain score reflects how much each participant contributes to the pattern expressed in each latent variable. Therefore, each latent variable consists of a singular image of voxel saliences (*i.e.*, a spatiotemporal pattern of brain activity), a singular profile of task saliences (*i.e.*, a set of weights that indicate how brain activity in the singular image is related to the experimental conditions, functional seeds, or behavioral/anatomical covariates), and a singular value (*i.e.*, the amount of covariance accounted for by the latent variable). There is no need for multiple comparison correction, as the activation patterns identified by PLS and corresponding brain responses is done in a single mathematical step (McIntosh et al., 2004).

The statistical significance of each latent variable was assessed using a permutation test, which determines the probability of a singular value from 500 random reorderings (McIntosh et al., 1996). Additionally, to determine the reliability of the saliences for each brain voxel, the standard error of each voxel's salience on each latent variable was estimated by 100 bootstrap resampling steps (Efron et al., 1985). Peak voxels with a bootstrap ratio (*i.e.*, salience/standard error) > 2.5 were considered to be reliable, as this approximates $p < 0.01$ (Sampson et al., 1989).

In the current study, we used two independent analyses; task PLS and seed PLS. First, we aimed to examine the whole-brain activity pattern during premise integration stage (second premise) considering the believability of the statements across both age groups. Second, we assessed age-related differences in the hippocampal functional network and its association with logical reasoning performance to examine whether the activity in the hippocampal network is modulated as a function of believability loads of second premise. As our aim was to explore the neural correlates of age-related differences during premise integration stage, our fMRI analyses focused on the second premise believability load, collapsing across believability load of the conclusion.

Whole-brain analysis (task PLS)

Whole-brain analysis focused on the onset times from the beginning of the *second* premise and included all three belief loads, depicted in Figure 2. Given that the logical reasoning task in this study was event-related, the activity at each time point in the analysis was normalized to activity in the first TR from second premise. Using this approach, we examined if the neural correlates for believable, unbelievable or neutral premises were different between younger and older adults. Thus, both age groups and three premise conditions were included in the analyses, simultaneously. This analysis revealed two latent variables and for clarity, we depicted the results of each LV and their positive/negative saliences in separate panels.

Brain-behavior connectivity analyses (Seed PLS)

We also examined task-related functional connectivity for hippocampal seed region and assessed the relationship with behavioral performance. To delineate the functional network involved during premise integration stage, signal intensity values from peak voxels of the seed were extracted and correlated with activity in the rest of the brain, as well as behavioral performance across all participants for believable and unbelievable premises. Our peak voxel (28 -37 -2) was selected based on its activity from the whole brain analysis and from previous functional reported in Neurosynth (Z score of 11.22) (Yarkoni et al., 2011). In an independent analysis to the task PLS, these correlations were then combined into a matrix and decomposed with singular value decomposition in a separate and independent analysis than whole-brain analysis. The seed PLS analysis results in sets of latent variables characterizing the sets of regions where the activity was correlated with the seed region for believable and unbelievable

premises. Permutation and bootstrap sampling were used to determine the significance and reliability of the functional connectivity analyses as in the whole brain analysis.

It has to be noted that only correct responses were included for the whole-brain and functional connectivity analyses because, first, our main aim was to investigate brain activation when participants correctly reached a reasonable conclusion in this experiment. Second, the ratio of incorrect responses was low. Finally, considering all combinations of belief load (believable or unbelievable conditions), validity of the syllogism (whether conclusion logically follow or doesn't follow premises), and participants' responses (accepting or rejecting conclusions) would lead to a high complexity of the design and analyses.

DWI acquisition and analysis

We used the FMRIB's Diffusion Toolbox (FDT) (Andersson et al., 2016) to correct our DWI images for eddy current distortion and head motion. Fractional Anisotropy (FA) in each voxel was estimated by first removing the non-brain tissues from the corrected images using the Brain Extraction Tool (Smith, 2002) and then locally fitting the diffusion tensor model at each voxel using the FDT. FA is a marker of the integrity of white matter tracts, reflecting the coherence within a voxel and fiber density (Alexander et al., 2007; Beaulieu, 2002). FMRIB's Linear Image Registration Tool (FLIRT) (Greve et al., 2009; Jenkinson et al., 2002; Jenkinson et al., 2001), with 12 degrees of freedom and trilinear interpolation, was used to realign the FA map of each subject with the standard brain template, MNI152 T1 1mm isotropic voxels. The affine transformation provided by this procedure ensures the transformed FA maps are in the same 3D coordinate system. We then generated the desired white matter mask for the cingulum bundle and the uncinate fasciculus using the ICBM-DTI-81 white-matter atlas (Hua et al., 2008; Oishi et al., 2010; Wakana et al., 2007). The average FA value in each tract was calculated and used in structure-behavior analysis.

Statistical analysis of behavioral data

It has to be noted that a high performance in this task is defined by a high ratio of correctly rejecting believable or correctly accepting unbelievable statements. Without loss of generality, we only considered correct rejection for our analyses as this value is the complement of correct acceptance when correct responses are included only. Hence, a high performance refers to a high rejection rate in believable statements and a low rejection rate in unbelievable

statements. The rejection rate was the number of times each participant correctly rejected a given syllogism divided by the total number of statements that should have been correctly rejected. Repeated measures ANOVA was performed for reaction times (RTs) and rejection rates as dependent variables. RTs were defined as the response times to decide during the conclusion stage; only correct responses were included for analyses relating to RT. A 3 (premise belief loads; believable, unbelievable, and neutral) by 2 (age group; younger and older adults) repeated measures ANOVA was conducted on RTs and rejection rates. Additional analyses on the conclusion stage have been included in the Supplementary Results.

Results

Behavioral results

Rejection rates

Repeated measure ANOVA on rejection rates revealed a significant main effect of premise belief load ($F(2,114) = 5.01$, $p = .008$, $\eta_p^2 = .08$), suggesting that believable premises had lower rejection rates relative to unbelievable and neutral ones ($t(58) = 2.95$, $p = 0.004$, $d = .77$ and $t(58) = 2.32$, $p = 0.02$, $d = .60$, respectively). A significant main effect of age group ($F(1,57) = 14.19$, $p = .000$, $\eta_p^2 = .19$) suggested that older adults had lower rejection rates relative to younger adults in all conditions. However, the interaction between age group and premise belief load did not reach significance ($F(2,114) = .40$, $p = .67$, $\eta_p^2 = .007$)

Reaction Times

Repeated measures ANOVA on reaction times showed non-significant main effect of premise belief loads ($F(2,114) = 2.16$, $p = .12$, $\eta_p^2 = .12$), age group ($F(1,57) = 31.83$, $p = .000$, $\eta_p^2 = .35$), and interaction between age group and premise belief load ($F(2,114) = 1.12$, $p = .32$, $\eta_p^2 = .019$).

FA values

There were significant differences between younger and older adults in both left (t(56) = 5.46, p= .000) and right (t(56) = 3.42, p= .001) uncinate fasciculus FA values, suggesting that older adults had lower FA values in this tract ($M_{left} = .25$, SD = .03; $M_{right} = .26$, SD = .04).

relative to younger adults (M_{left} = .30, SD = .02; M_{right} = .29, SD = .02). There was no age-related difference in the white matter FA values of the cingulum bundle (left: t(56) = .95, p= .34; Right: t(56) = .19, p= .84).

fMRI results

Whole-brain analyses

Age-related differences between believable and unbelievable premises

To determine age-related differences in beleivable and unbeleivable premises, the whole-brain results were conducted on the premise integration stage and revealed two latent variables. The first accounted for 68% of the covariance of the data (*p* = .000) and included right superior frontal gyrus, right anterior cingulate cortex (ACC), bilateral inferior frontal gyrus (IFG), left insula, left inferior parietal lobe, left precuneus, and left caudate. These regions were recruited by younger adults only, irrespective of the belief load of the premise (Table 2).

[Insert Table 2 about here]

The second latent variable accounted for 10% of the covariance of the data and distinguished neutral conditions from believable/unbeleivable conditions in older adults only (*p* = .048). One network included the left IFG, right insula, right middle frontal gyrus, left posterior cingulate cortex, and right hippocampus. These regions showed enhanced activity in older adults, whereas younger adults did not recruit these regions reliably. Older adults recruited these regions for both believable and unbelievable premises more than for neutral ones (Figure 2). Older adults also recruited a distinct sets of regions including right ACC, right superior frontal gyrus, and left middle frontal gyrus for neutral premisses relative to other conditions (Table 3).

[Insert Figure 2 & Table 3 about here about here]

Brain-behavior connectivity results

Age-related differences in hippocampal functional network during premise integration

The brain-behavior connectivity analyses using the hippocampus as a seed with behavioural performance were conducted and revealed two significant latent variables. First

latent variable accounted for 26% of the covariance of the data (p = .000) and yield a network which was connected to the hippocampus for both believable and unbelievable conditions among younger adults without contributing to the performance. This network was connected to the hippocampus and also contributed to the performance – higher rejection rates – among older adults during believable condition. This network included anterior cingulate, bilateral postcentral gyrus, right middle frontal gyrus, right superior parietal lobe, and right precuneus.

The second latent variable accounted for 14% of the covariance of the data (p = 0.042) and yield a network, which included anterior cingulate, left inferior frontal gyrus, bilateral insula, left superior temporal gyrus, bilateral precentral gyrus, left angular gyrus, left parahippocampus, left hippocampus, bilateral thalamus, posterior cingulate gyrus, precuneus, and bilateral lingual gyrus (Figure 3). This network was engaged by older adults only during believable condition and contributed to higher rejection rates for believable conditions among this age group.

[Inset Figure 3 about here]

Age-related differences in structural integrity of cingulum bundle for premise integration

To provide additional information on the structural integrity of the underlying hippocampal networks, analyses on white matter tracts (cingulum bundle) and behavioural responses (rejection rates of syllogisms) were conducted and revealed a negative correlation between cingulum bundle integrity and rejection rates among younger adults (left cingulum bundle: $r(29) = -.44$, $p = .017$; right cingulum bundle: $r(29) = -.39$, $p = .033$), suggesting that younger adults who had higher integrity in the cingulum, rejected the *unbelievable* premises less.

A positive correlation was found between rejection rates of *believable* premises and cingulum integrity among older adults (left cingulum: $r(29) = .38$, $p = .038$; Table 4), suggesting that older adults who had higher integrity in the left cingulum bundle, rejected the *believable* premises more. No other correlations were found between integrity of the uncinate fasciculus and performance (all ps > .05). None of the correlations were significant with RTs.

[Insert Table 4 about here]

Discussion

The present study lends evidence for the age-related differences in logical reasoning and the impact of currently-held beliefs using a syllogism task. First, the whole-brain results from premise integration stage (second premise) showed that while younger adults recruited a single network for all conditions, older adults' brain activity was modulated by the believability load of the premise. Our functional connectivity results using the hippocampus as a seed revealed that older adults engaged a hippocampal network for believable premises and this network contributed to higher rejection rates, suggesting more controls over their currently-held beliefs and better logical reasoning performance overall for believable inferences only. This network specifically included anterior cingulate and inferior frontal gyrus, regions that are involved in cognitive control and inhibitory control. Furthermore, our structure-function analyses suggested a positive correlation between cingulum bundle structural integrity and rejection rates for believable inferences, that is, the higher the integrity in the cingulum bundle was associated with the higher the rejection rates in believable inferences among older adults. In sum, our results using multimodal imaging; behavioral performance, functional connectivity, and white matter structural integrity together support the compensatory role of hippocampus-prefrontal areas contributing to inhibition of currently-held beliefs during a logical reasoning task among older adults.

Behavioral findings

Our behavioral results showed higher rejection rates for unbelievable premises than believable and neutral ones. Higher rates of rejection for unbelievable statements is related to the existing theories, such as mental model theory, that individuals construct mental models from syllogisms. If the belief load of the syllogisms conflicts with the mental model, it initiates a search for an alternative model of the premises (Johnson-Laird, 2001; Johnson-Laird, 2010; Johnson-Laird et al., 2015). Our results extend previous studies, which have been mainly focused on the believability load of the conclusion, and suggest that even during the unbelievable premises, the cognitive control might be triggered which lead to differences in response.

Age-related differences during premise integration

To our knowledge, this study is the first to examine neural correlates of logical reasoning in late adulthood and to report the role of IFG, and the hippocampus (see the following section),

during premise integration stage using a syllogistic reasoning task. Our whole-brain analysis showed that older adults activated several brain areas including left IFG during premise integration condition, more so for believable and unbelievable conditions than neutral one. The importance of the IFG region has been shown in number of tasks including logical reasoning (Goel et al., 2003; Prado et al., 2011) and cognitive control (Brass et al., 2005; Derrfuss et al., 2005) when the tasks are complex and attentional demand is high. There is neuroimaging evidence that in addition to the inhibitory control (Aron et al., 2014), the IFG is also involved in rehearsal system of working memory (McDermott et al., 2003). During the syllogistic reasoning task, information is needed to be retrieved from memory and currently-held beliefs are required to be inhibited to make sound logical decisions. We have shown that IFG plays a central role in this process during premise integration stage. While previous studies reported the role of IFG during conclusion stage with various believability loads, our findings take these studies further and suggest that IFG contributes to the inhibition of current beliefs during premise integration stage in addition to the conclusion stage reported previously. Our results are also in line with findings from Tsuji and colleagues (Tsujii et al., 2010), indicating enhanced IFG among older adults using near-infrared spectroscopy method.

Age-related differences in hippocampal functional network during premise integration

Growing body of studies have shown that hippocampal structural and functional changes contribute to the memory and cognitive performance and, thus, are especially important in late adulthood. In addition to the substantial structural changes in the hippocampus and medial temporal cortex volume, which differentiate between healthy and pathological (e.g. AD) aging (Desikan et al., 2006), structural and functional connectivity between hippocampus and frontal regions go under substantial changes in aging (Fjell et al., 2010). In our task, the engagement of the hippocampus during premise stage suggests that there is a need to compare the belief content of syllogisms with current beliefs stored in the memory during a logical decision making. Previous studies have suggested that the hippocampus can detect deviant stimuli from their context in the environment (Barbeau et al., 2017; Grunwald et al., 1998), and can detect a mismatch from a novel sequence of events (Garrido et al., 2015). When faced a logical reasoning task, individuals are required to retrieve semantic knowledge and subsequently, to compare them with assumptions presented at syllogisms. Given the importance of the hippocampus in semantic memory (Manns et al., 2003), our findings offer empirical evidence to the idea that the

hippocampus, and its connection with prefrontal areas, is involved in premise integration stage possibly via retrieval-mediated learning. Our results also suggest that age-related changes in the reasoning might be due to the underlying changes in the hippocampal structure and function. However, further investigation is needed to determine the differential role of hippocampus and its connection to PFC in various forms of complex reasoning tasks and in different stages of reasoning including conclusion stage.

In our functional connectivity findings, older adults engaged the hippocampus network that which included anterior cingulate and inferior frontal gyrus, more for believable premises and this network contributed to correctly rejecting believable assumptions (i.e. higher logical reasoning performance). The engagement of the hippocampus-prefrontal network for believable premises highlights the importance of retrieving semantic associations when the belief load is congruent with currently-held beliefs (Wendelken et al., 2010) and suggests that this network is pivotal in controlling currently-held assumptions and in reaching a logically correct conclusion. The contribution of this network to performance among older adults corroborate the view of engaging a compensatory network by advancing age (for reviews see (Davis et al., 2008; Grady, 2012; Ziaei et al., 2016). Interestingly, a recent study showed that age-related decline in memory-dependent decisions can be diminished by a compensatory network between ventromedial and dorsolateral PFC regions (Lighthall et al., 2014). This over-recruitment of frontal areas during believable condition observed in this study, also highlights that functional compensation of PFC regions may be a protective mechanism during the logical decision when rejection of believable assumptions is required.

Another important point in relation to the hippocampal activity is that various parts of hippocampus are involved in rather different tasks. The coordinates for this study was from the posterior part of the hippocampus. Our results are in line with previous reports about the posterior hippocampus to work in concert with regions involved in imagery and perceptual processing to form mental constructions via relational processing (Sheldon et al., 2016a; Sheldon et al., 2016b). Strange and colleagues (1999) also reported the anterior–posterior familiarity gradient, suggesting that increase in familiarity leads to activation of the posterior hippocampus. Given all the categories in the believable condition are familiar categories (e.g., furniture, fruits, animals), different networks might be involved in reasoning about familiar or unfamiliar concepts; i.e. believable vs. unbelievable conditions. Future studies, thus, are needed to

distinguish between anterior and posterior divisions of the hippocampus during a logical reasoning task.

Age-related differences in structural integrity of cingulum bundle for premise integration

The age-related changes in macrostructural brain properties lead to decreased volumes and thickness in the prefrontal and temporal regions, specifically the prefrontal cortex and hippocampus, which are among well-established findings (Persson et al., 2012). Accumulating evidence have reported the link between the integrity of various white matter pathways and cognitive performances such as response time (Madden et al., 2009); task switching performance (Gold et al., 2010); working memory (Burianová et al., 2015); motor performance; and problem solving (Zahr et al., 2009). Specifically, studies have supported the role of cingulum bundle in tasks associated with visuospatial processing and memory (Davis et al., 2009). Our results are in line with these reports and suggest that, for older adults, FA values derived from cingulum bundle were positively correlated with the rejection rate of the believable inferences and negatively correlated with the rejection rate of the unbelievable inferences. This finding suggests that a higher integrity in this tract leads to more logically correct decisions which are less bounded by the belief load of the premises, hence, a better logical reasoning performance. Given that this is the first study to investigate the relation between structural and functional networks in logical reasoning, these results should be considered preliminary and interpreted cautiously. Further investigation is needed to provide conclusive evidence for the role of cingulum in logical reasoning.

Future directions

It has to be noted that one limitation of this study is the sample size for correlational analyses between cingulum bundle FA values and behavioral measures. Further studies are warranted to replicate the correlational findings in a larger sample size. Additionally, future studies should investigate the role of cortical and subcortical areas in different forms of reasoning such as abductive reasoning. Lastly, as mentioned previously, our results included only correct responses to the syllogisms. It will be informative for future studies to include incorrect responses to the syllogistic reasoning and investigate corresponding brain networks.

Conclusion

The primary aim of this study was to investigate the hippocampal-prefrontal functional networks involved in logical reasoning and inhibition of beliefs. For the first time, we have shown that older adults brain activity was modulated by the belief load during premise integration stage. Functional connectivity results with the hippocampus revealed that older, but not younger, adults engaged a hippocampal-PFC network which contributed to higher reasoning performance for believable inferences. Additionally, our structure-function connectivity analyses showed that cingulum bundle integrity correlated with logical reasoning performance for believable inferences in older adults' group. These novel results highlight the importance of the integrity of retrieving semantic information during a logical reasoning task and suggest a compensatory role of hippocampus-PFC network during a reasoning task. This study provides new insights for the relation between semantic memory, inhibitory control, and logical reasoning in aging, which can be utilized to design appropriate intervention for improving logical reasoning performance.

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Figure Legends

Figure 1. The timing and example of the experimental design. In this experiment, participants were presented with the first premise for two seconds followed by the second premise that was shown for 4 seconds. During the conclusion presentation, 12 seconds, participants were asked to choose if the conclusion follows the two premises or not, using the MRI compatible response box. Onsets from the second premise were only used to assess brain activity during premise integration.

Figure 2. Whole-brain results during premise integration. Onsets of the second premise were used in this analysis. All believable, unbelievable, and neutral premises were included in this analysis. ***(a)***, Younger adults recruited the blue regions similarly for all conditions during the premise stage. ***(b)***, Older adults, however, recruited these yellow regions more during unbelievable and believable premises. ***(c)***, these regions were more involved during neutral premises relative to other conditions among older adults. All reported regions have bootstrap ratio of ≥ 2.5 and cluster size ≥ 50 voxels. Abbreviations: L = left hemisphere, R = right hemisphere.

Figure 3. Hippocampal functional connectivity results among older adults. Onsets of the premise stage were used for this analysis. ***(a)*** The functional network connected to the hippocampus during the premise integration stage. Panel ***(b)*** and ***(c)*** show correlations between activity in hippocampal brain network and behavioral performance among younger and older adults, respectively. All reported regions have a bootstrap ratio ≥ 3 and cluster size ≥ 50 voxels. Abbreviations: HC = hippocampus, L = left hemisphere, R = right hemisphere.

Figure 1

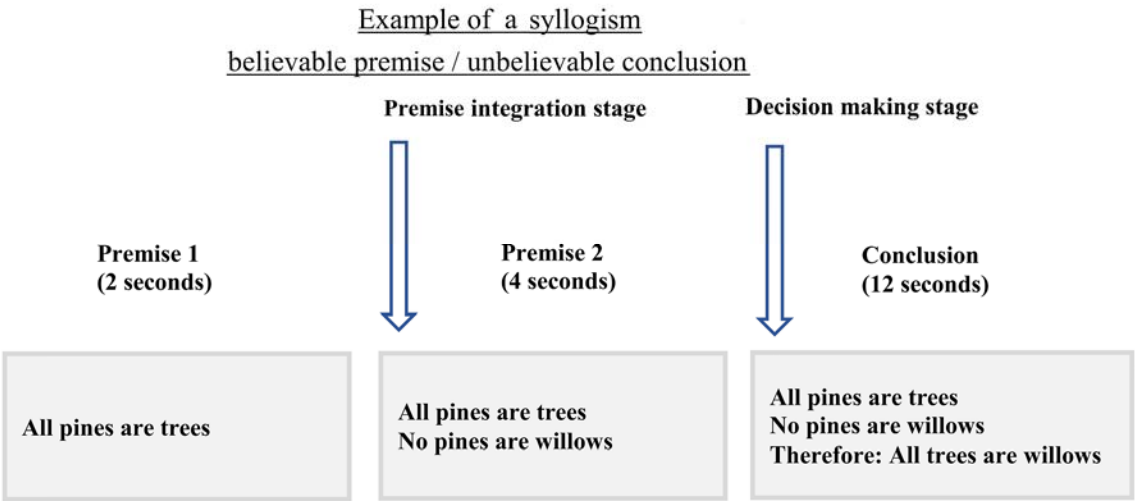

Example of a syllogism
believable premise / unbelievable conclusion
Premise integration stage
Decision making stage
Premise 1
(2 seconds)
Premise 2
(4 seconds)
Conclusion
(12 seconds)
All pines are trees
All pines are trees
No pines are willows
All pines are trees
No pines are willows
Therefore: All trees are willows

Figure 2

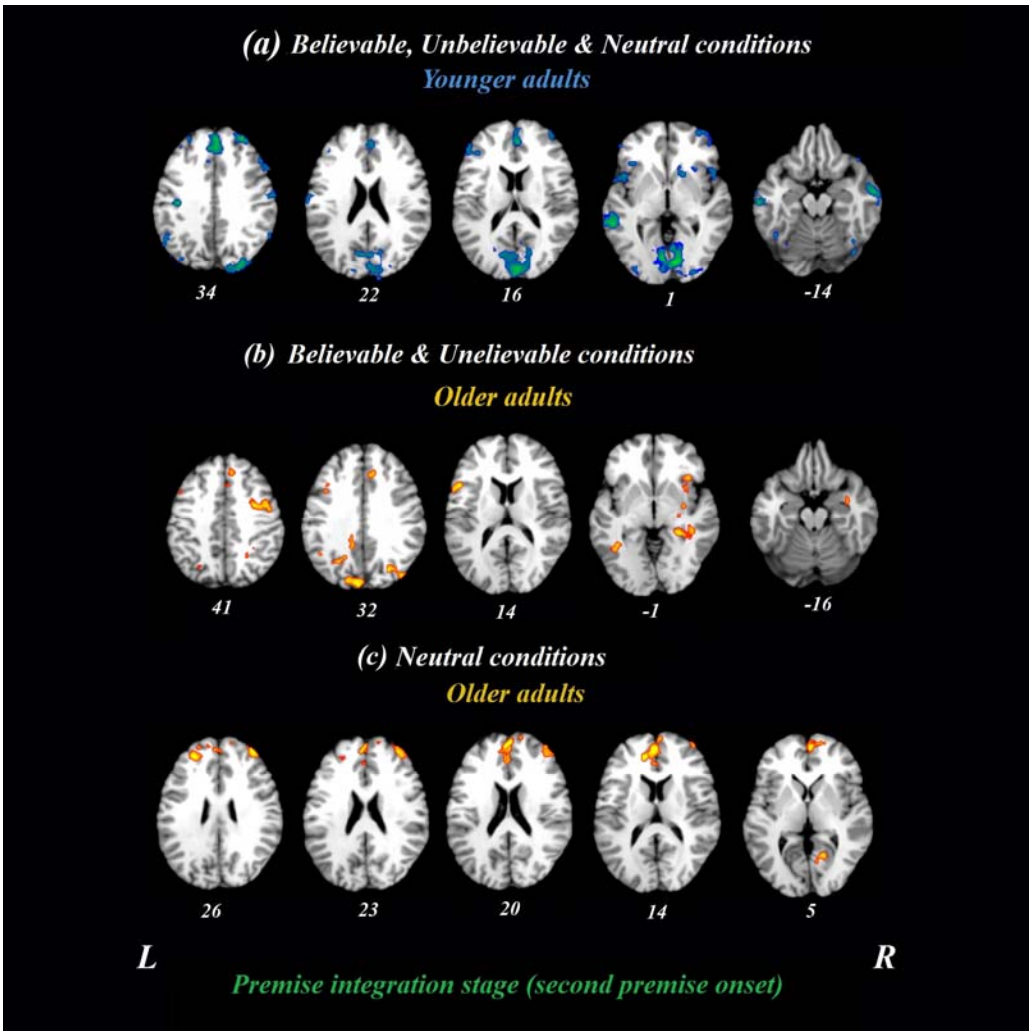
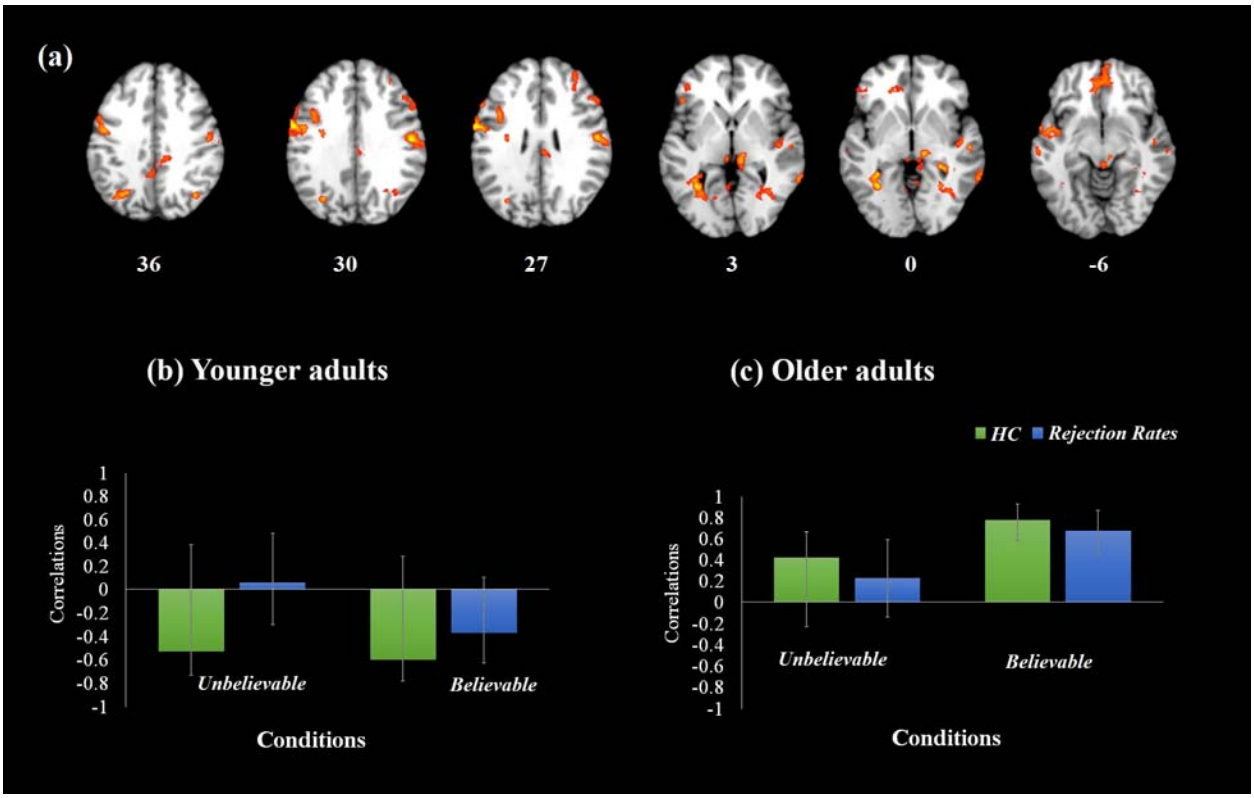

(a) Believable, Unbelievable & Neutral conditions
Younger adults
34
22
16
1
-14
(b) Believable & Unelievable conditions
Older adults
41
32
14
-1
-16
(c) Neutral conditions
Older adults
26
23
20
14
5
L
R
Premise integration stage (second premise onset)

Figure 3


(a)
36
30
27
3
0
-6
(b) Younger adults
(c) Older adults
HC
Rejection Rates
Correlations
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1
Unbelievable
Believable
Conditions

Tables

Table 1. Descriptive and inferential statistics of performance on background measures and logical reasoning task

Measurements	Younger adults Mean (SD)	Older adults Mean (SD)	Inferential statistics *t (df)*
Age	21.13 (2.72)	70.66 (4.21)	5.79 (57)**
Education (yrs)	15.28 (1.97)	16.50 (4.07)	1.40 (51)**
NART FSIQ	112.02 (4.77)	119.47 (4.99)	5.51(56)****
Trail Making Test (sec)			
Trail A	18.14 (5.24)	27.43 (5.86)	6.40 (57)****
Trail B	40.05 (12.55)	53.04 (13.44)	3.83 (57)****
B-A index	21.90 (10.34)	25.61 (13.00)	1.20 (57)**
DASS – 21			

Stress		6.06 (5.19)	5.06 (4.83)	0.76 (57)**
Anxiety		2.68 (3.55)	1.60 (2.54)	1.35 (57)**
Depression		3.31 (4.60)	1.66 (2.92)	1.64 (57)
Stroop test (sec)				
Congruent		0.72 (0.12)	1.24 (0.23)	10.69 (57)**
Incongruent		0.82 (0.16)	1.46 (0.36)	8.68 (57)**
Neutral		0.70 (0.10)	1.13 (0.19)	10.50 (57)**
Stroop effect		0.16 (0.12)	0.29 (0.21)	2.88 (57)*
Reasoning performance based on premise conditions				
RT (sec)	Unbelievable	4.733 (1.13)	5.73 (1.56)	5.46 (57)**
	Believable	4.655 (1.02)	5.65 (1.53)	5.83 (57)**
	Neutral	4.791 (1.00)	5.81 (1.50)	4.95 (57)**
Rejection	Unbelievable	0.98 (0.13)	0.86 (0.20)	2.52 (57)*
	Believable	0.93 (0.07)	0.77 (0.17)	4.49 (57)**

Neutral	0.97 (0.13)	0.83 (0.24)	2.70 (57)*

*$p < 0.05$, **$p < 0.005$. NART FSIQ = National Adult Reading Test Full-Scale Intelligence Quotient; Stroop effect = (Incongruent – neutral/neutral); DASS-21 = Depression, Anxiety, Stress Scale; sec = second; SD = standard deviation; M = mean; *t* = two-sample t test.

Table 2. Whole-brain results showing regions activated for all conditions among younger adults during the premise integration stage

Regions	Hem	Cluster size	MNI coordinates XYZ	BSR
All conditions – premise integration stage				
Superior frontal gyrus	R	19027	16 34 54	-8.0285
Medial cingulate cortex	L	117	-4 -20 36	-4.2812
Middle cingulate cortex	R	104	14 -42 36	-4.3166
Inferior frontal gyrus (p. Triangularis)	L	381	-48 40 14	-5.1408
Inferior frontal gyrus (p. Opercularis)	R	232	50 12 0	-4.9558
Middle orbital gyrus	R	60	6 32 -10	-5.1013
Superior medial gyrus	L	16156	-2 32 52	-8.5392
Superior medial gyrus	R	180	0 54 6	-5.1678
Insula lobe	L	603	-28 22 8	-6.2758
Superior temporal gyrus	L	70	-62 -46 16	-4.0708
Middle temporal gyrus	L	785	-58 -38 2	-6.0463
Middle temporal gyrus	R	564	58 -10 -18	-5.5045
Medial temporal gyrus	L	857	-56 -40 2	-6.953

Medial temporal gyrus	R	787	66 -14 -12	-5.2644
Inferior parietal lobule	L	250	-42 -80 26	-5.336
Thalamus	R	59	16 -14 -4	-5.4105
Putamen	R	544	16 12 -2	-5.7981
Caudate	L	51	-20 0 22	-4.8374
Precuneus	L	81	-14 -52 54	-4.29
Cerebellum	R	92	22 -52 -18	-4.9426

Hem = hemisphere; BSR = bootstrap ratio; MNI = Montreal Neurological Institute.

Table 3. Whole-brain results showing regions modulated by the belief among older adults during the premise integration stage

Regions	Hem	MNI coordinates XYZ	BSR
Unbelievable & believable > Neutral			
Middle cingulate cortex	R	10 32 34	3.898
Middle frontal gyrus	R	36 20 40	3.9517
Inferior frontal gyrus (p. Opercularis)	L	-54 12 12	4.1645
Insula lobe	R	38 18 -8	3.8756
Posterior cingulate cortex	L	-10 -44 28	4.4265
Cuneus	L	-8 -84 28	4.5638
Putamen	R	34 -8 -8	4.7225
Hippocampus	R	28 -38 -2	4.0095
Neutral > Believable and Unbelievable			
Superior frontal gyrus	R	30 24 58	-4.3859
Superior medial gyrus	R	2 56 4	-5.4506
Anterior cingulate cortex	L	-8 44 16	-3.5899
Middle frontal gyrus	R	36 50 24	-4.3307
Middle frontal gyrus	L	-28 48 28	-5.2424

Hem = hemisphere; BSR = bootstrap ratio; MNI = Montreal Neurological Institute

Table 4. Pearson correlation between Cingulum tract FA value and rejection rates in both age groups

	Younger adults		Older adults	
	r	*df*	*r*	*df*
Rejection rates (Believable premise)				
Right Cingulum	.033	29	.246	29
Left Cingulum	-.019	29	**.388**	29
Right Uncinate Fasciculus	.017	29	.225	29
Left Uncinate Fasciculus	.012	29	.352	29
Rejection rates (Unbelievable premise)				
Right Cingulum	**-.396**	29	-.075	29
Left Cingulum	**-.441**	29	.001	29
Right Uncinate Fasciculus	.018	29	-.220	29
Left Uncinate Fasciculus	.212	29	-.161	29
Rejection rates (Believable conclusion)				
Right Cingulum	-.190	29	.200	29
Left Cingulum	-.191	29	.249	29
Right Uncinate Fasciculus	.028	29	.207	29
Left Uncinate Fasciculus	.088	29	.345	29
Rejection rates (Unbelievable conclusion)				
Right Cingulum	-.208	29	.124	29
Left Cingulum	-.266	29	.296	29
Right Uncinate Fasciculus	.157	29	-.148	29
Left Uncinate Fasciculus	.144	29	-.041	29

Note: Bold numbers indicate significant level less than 0.05.