Age association of language task induced deactivation induced in a pediatric population

Binjian Sun a, Madison M. Berl b, Thomas G. Burns c, William D. Gaillard b,d, Laura Hayes a, Malek Ad Jouadi e, Richard A. Jones a,f,⁎

a Department of Radiology, Children's Healthcare of Atlanta, Atlanta, GA, USA
b Center for Neuroscience, Children's National Medical Center, Washington, DC, USA
c Department of Neuropsychology, Children's Healthcare of Atlanta, Atlanta, GA, USA
d NIH, NINDS Clinical Epilepsy Section, Bethesda, MD, USA
e College of Engineering and Computing, Florida International University, Miami, FL, USA
f Department of Radiology, Emory University, Atlanta, GA, USA

ARTICLE INFO
Article history:
Accepted 30 September 2012
Available online 12 October 2012

Keywords:
fMRI-Functional Magnetic Resonance Imaging
DMN-Default Mode Network
TID-Task Induced Deactivation
fcMRI-Functional Connectivity MRI

ABSTRACT
Task-induced deactivation (TID) potentially reflects the interactions between the default mode and task specific networks, which are assumed to be age dependent. The study of the age association of such interactions provides insight about the maturation of neural networks, and lays out the groundwork for evaluating abnormal development of neural networks in neurological disorders. The current study analyzed the deactivations induced by language tasks in 45 right-handed normal controls aging from 6 to 22 years of age. Converging results from GLM, dual regression and ROI analyses showed a gradual reduction in both the spatial extent and the strength of the TID in the DMN cortices as the brain matured from kindergarten to early adulthood in the absence of any significant change in task performance. The results may be ascribed to maturation leading to either improved multi-tasking (i.e. reduced deactivation) or reduced cognitive demands due to greater experience (affects both control and active tasks but leads to reduced overall difference). However, other effects, such as changes in the DMN connectivity that were not included in this study may also have influenced the results. In light of this, researchers should be cautious when investigating the maturation of DMN using TID. With a GLM analysis using the concatenated fMRI data from several paradigms, this study additionally identified an age associated increase of TID in the STG (bilateral), possibly reflecting the role of this area in speech perception and phonological processing.

© 2012 Elsevier Inc. All rights reserved.

Introduction

Task-induced deactivation (TID), or negative BOLD response, observed during functional MRI experiments have been studied for many years and were formalized as the default mode network (DMN) by Raichle et al. over a decade ago (Raichle et al., 2001). The deactivated regions are largely independent of the fMRI task paradigms and typically include the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), orbital frontal gyrus (OFG), anterior cingulate cortex (ACC) and the precuneus. Alternatively, thanks to the observation that cortical regions within the DMN exhibit spontaneous temporal signal synchrony in the resting state (Biswal et al., 1995), the DMN can also be localized using functional connectivity MRI (fcMRI) derived from correlation (Greicius et al., 2003) or independent component analysis (Greicius et al., 2004). Generally, TID and fcMRI offer a converging, yet distinctive, analysis of the DMN (Mannell et al., 2010; Thomason et al., 2008). In this article, we will concentrate on changes in the TID that occur as children mature into adults.

The DMN is assumed to be involved in monitoring the external environment and engaging in internally directed mental processes such as self-reflection (Buckner et al., 2008). Early studies have reported altered DMN in a number of diseases including, but not limited to, autism (Kennedy et al., 2006) and Alzheimer’s disease (Greicius et al., 2004; Lustig et al., 2003). In light of these findings, neuroimaging of the DMN has emerged as an area of active research. The neurodevelopment of DMN in children and adolescents is particularly interesting since many of the cognitive functions associated with the DMN, such as episodic memory and theory of mind, rapidly evolve in this population. In adults, the effect of aging on the DMN has been investigated in multiple studies (Grady et al., 2006; Lustig et al., 2003; Persson et al., 2007; Sambataro et al., 2010) with a common finding that both the TID and the functional connectivity within the DMN is inversely correlated with age. For example, using a semantic classification paradigm, Lustig et al. (2003) observed reduced deactivations in the mPFC,
PCC and parieto-temporal in older adults compared to their younger counterparts. Furthermore, a reduced TID often coincided with worse task performance in older adults. These findings suggest that by not deactivating the DMN during task engagement, there is a possible negative effect on the allocation of the cognitive resources required for performing a task.

Compared to the effect of aging on the DMN, the development and maturation of the DMN in a pediatric population has received less attention. Using a Stroop task fMRI paradigm, Marsh et al. reported that TIDs in ACC, mPFC, and PCC were positively correlated with age (Marsh et al., 2006). The authors postulated that this could reflect enhanced engagement in self-monitoring and free associative thought processes during baseline tasks for adults compared to children. However, it is worth noting that the paradigm used for that study was not adapted according to either the age or intelligence of the participants, i.e. the same Stroop task was administered to all participants. Another study applied TID and functional connectivity approaches to separate participant cohorts in order to study the DMN in children, and compared the results to the characteristics of adult DMN from the literature (Thomason et al., 2008). In this study, the difficulty of fMRI paradigm was matched with the cognitive level for each participant. For both TID and fcMRI, the investigators noticed developmental effects in the DMN. Briefly, while adults and children shared many areas of the DMN, including the PCC, lateral parietal cortex and mPFC, children were also shown to have distinctive TIDs at the Brodmann areas 3, 13 and 18. The developmental impact on DMN connectivity were further assessed by Fair et al. with analyses of resting state fMRI data (Fair et al., 2008). By comparing the DMN in terms of connectivity strength between children (7–9 years old) and adults, this study observed evidence of enhanced connectivity within the DMN in adults. These results were later substantiated by a DMN connectivity investigation (Supekar et al., 2010) that combined fcMRI, voxel-based morphometry (VBM), and DTI analyses. In this study, Supekar et al. demonstrated that the major DMN nodes are readily detected in children aged from 7 to 9 years old. Interestingly, both anatomical and functional connectivity between mPFC and PCC was shown to be weaker in children, whereas for the PCC and the left medial temporal lobe (MTL), only the anatomical connectivity exhibited age association. In the few studies that investigate the developmental differences of the DMN in children, the strength of resting state connectivity within DMN appears to increase with age. Taken together with performance differences related to deactivation, this developmental change may be related to ongoing refinement of cognitive skills that occurs during development.

Mannell et al. recently demonstrated that the DMN detected by task induced deactivation tends to be more spatially confined than those detected by rs-fcMRI (Mannell et al., 2010), possibly reflecting interactions between neural networks. The same trend has also been observed in other studies (Thomason et al., 2008). Furthermore, several TID studies have demonstrated the dependency of TID on cognitive load (Esposito et al., 2006; Supekar et al., 2009; Tomasi et al., 2006), and observed a positive relationship between the strength of the TID and the level of cognitive load. Since the mechanism underlying TID is believed to be the suppression of default mode connectivity by the fMRI tasks, it is plausible that the difficulty of the task affects the TID. In other words, interactions between DMN and the fMRI target network can be manifested in the TID. More interestingly, as the developmental impact of various diseases and developmental disorders.

The current study aims to investigate the interactions between the DMN and language network in pediatric population by applying a TID analysis to a range of language fMRI data acquired on normal children. It is hypothesized that the age association of TID reflects contributions from both the resting state DMN connectivity and the suppression of the DMN connectivity during an active task.

Materials and methods

Participants and acquisition parameters

Participants for this study were recruited at Children’s Healthcare of Atlanta (CHOA) and Children’s National Medical Center (CNMC). The fMRI data were acquired as control data for the Multi-Site Pediatric Network for fMRI Mapping in Childhood Epilepsy consortium (You et al., 2011). Both sites used the same model of scanner (Siemens 3 T Trio) and identical imaging parameters, and a study utilizing the same datasets demonstrated minimal data differences across sites and scanners (You et al., 2011). Standard Wechsler Abbreviated Scale of Intelligence (WASI) tests were scheduled, but not enforced (to facilitate participant recruitment), for all subjects in order to collect the IQ scores. The fMRI acquisitions were performed using a gradient echo EPI sequence with TR = 3 seconds and TE = 36 milliseconds. In addition, a high-resolution T1 weighted anatomical volume was acquired for each participant to facilitate inter-subject registration. The study was approved by the Institutional Review Boards at CHOA, CNMC, and FIU.

fMRI paradigms

The fMRI paradigms involved both single word and whole language approaches adjusted for the cognitive ability of the participants. The paradigms were designed to target both expressive and receptive language processing and were developed for the assessment of the BOLD response in the language cortex of children and young adults under clinical conditions (Berl et al., 2010; Mbwana et al., 2009). Specifically, the following three tasks were employed, each using a block design:

a) Auditory category decision task (AUDCAT): A category is presented followed by a series of words. Participants are instructed to press a button if a word belongs to the specified category.

b) Auditory description decision task (ADDT): A description of an object is presented to the participants. The participants are required to press a button when the description matches the object.

c) Listening to stories (Listening): Stories based on standardized measures of reading including the Gray Silent Reading Test and DIBELS are presented with pseudorandom beeps inserted into the story. Participants are instructed to press a button when a beep is heard while listening to the story. The participants are told that they will be asked questions about the story after the scan to try and ensure that the participant paid attention to the story.

The rest condition for all three paradigms consisted of reverse speech version of the experimental condition with intermittent beeps as cues for button presses. All paradigms comprised five 30-second task blocks and five 30-second control (rest) blocks, resulting in a total duration of five minutes. Participants were instructed to press a single button for correct answers or upon hearing a beep (70% true and 30% foils for task condition, matching number of button pushes for the corresponding control condition) during the course of the experiment. The responses were collected and inspected for the purposes of task monitoring and evaluation of response accuracy. When a participant was deemed not to be following the fMRI paradigms, as indicated by their responses, they would be retrained and rescanned with a different version of the fMRI paradigm. The paradigms were graded for skill and the appropriate version was selected for each participant based on his/her neuropsychological test score. Such arrangement ensures that the task difficulty level is comparable for all studied subjects. The paradigms were implemented with E-prime (Psychology Software Tools, Inc., Sharpsburg, PA USA) and were presented aurally to the
participants via headphones. The ADDT does not have an explicit memory component, whereas the AUDCAT has a limited memory component (remembering the category for the duration of the task). Comparatively, the listening task requires most memory functioning as the subject was told that they would be questioned about the stories after the scan.

Data analysis

Pre-processing

The DICOM MRI data were first converted to NIFTI format with MRIConvert (http://lcni.uoregon.edu/~jolinda/MRIconvert/), and then pre-processed using FSL (Smith et al., 2004). Specifically, the pre-processing steps included motion correction, spatial noise suppression, temporal filtering and spatial normalization. Motion correction was carried out employing the MCFLIRT tool of FSL. Following motion correction, the 4D fMRI data were spatially (FWHM = 5 mm) and temporally filtered (high pass with a cutoff of 0.01 Hz). Finally, the data were registered to the MN152 brain template using an affine transformation (12 degree of freedom) implemented in the FLIRT tool of FSL. Although intensity normalization was not carried out (following FSL recommendation), each individual result was scaled with its grand mean for later group analysis. The same pre-processing was applied to the fMRI data of all participants. Once the pre-processing was complete, the motion correction results were reviewed in order to detect participants with excessive motion during the acquisition. Data from participants containing motion greater than 1 mm along LR, AP or IS directions were excluded from further processing, leaving data from 45 participants for analysis.

GLM analysis

The pre-processed data that passed the motion exclusion criterion were subject to lower (individual) level statistical analysis. Briefly, GLM based univariate statistical test (Z threshold of 2.3 and cluster p threshold of 0.05) was carried out to identify voxels that were significantly deactivated/activated during the task session. Lower level results were then fed to a higher (group) level analysis. The higher level GLM analysis uses FLAME 1 mixed effects, and again thresholds at z > 2.3 and cluster p < 0.05 (FSL defaults).

Two strategies were pursued for the higher level analysis of the influence of age: 1) the development of DMN was assumed to be linearly dependent on age, which was demeaned in the GLM analysis, and this contrast was inspected to evaluate the age association of the TID. The group difference maps were contrast masked (i.e., the group 1 minus group 2 contrast was masked by the group 1 mean contrast), and confidence level was chosen to be 95% (i.e., p < 0.05). The analysis was conducted utilizing the dual regression tool of FSL made available by Beckmann and Smith at the FMRIB Centre, University of Oxford.

ROI analysis

While the GLM analysis reveals the spatial extent of the deactivation, it may not be suitable for evaluating the strength of deactivation. To more accurately capture the changes in the strength of the cortical deactivation from childhood to adolescence, a ROI based analysis similar to that used by Marsh et al. was performed (Marsh et al., 2006). Specifically, two 40 mm cubic ROIs containing mPFC/ACC and PCC/precuneus respectively (both of these areas consistently exhibit deactivations on the mean fMRI deactivation maps for the AUDCAT, ADDT and listening paradigms) were manually chosen in the standard template space. The paradigm- and age-independent ROIs were selected based on the mean deactivation maps from all fMRI paradigms as derived using the GLM model with age as an independent variable and were made sufficiently large to account for task and individual variability in DMN location. A retrospective inspection ensures that the ROIs cover at least 70% of the TID clusters (for mPFC/ACC and PCC/precuneus, respectively) for all participants. All individual level data were preprocessed and registered to a standard 2 mm MNI brain template prior to the ROI extraction. The DMN regions in the parieto-temporal cortex were excluded from this analysis due to the great variability of the TID in this region across the study population. For each participant, the time course of every voxel in each ROI was extracted and correlated with the expected deactivation pattern. The deactivation pattern was generated by convoluting the boxcar deactivation paradigm with a canonical hemodynamic response function (delay of response = 6 s, delay of undershoot = 16 s, disperse of response and undershoot = 1 s, and ratio of response to undershoot = 6). The ROI data were then “correlation filtered” by rejecting voxels whose temporal correlation coefficients with the deactivation time course were < 0.1. This procedure ensures that only voxels which exhibited deactivation inside the selected ROIs were analyzed. Subsequently, the time courses of the surviving voxels (i.e., correlation coefficient ≥ 0.1) in each ROI were averaged, and the mean percentage differences between baseline and task blocks of the averaged signal in each ROI were calculated for all 45 participants and used as an indication of the strength of the TID. The combination of large ROI and correlation filtering allowed for the inclusion of DMN for each participant while taking into account the inter-individual variability.

The relationship between age (independent variable) and percentage signal difference (dependent variable) was modeled using least mean squares linear fit in order to reveal any trend in the deactivation strength with age. The coefficient of determination ($r^2$) and Pearson correlation (r) of the fitting were computed, and r was statistically tested for significance using Fisher’s Z transformation. Additionally, we applied unpaired t-test based on the two groups to

Dual regression analysis

In addition to GLM analysis, we also compared the young and old participants groups described in the previous section using a recently developed ICA technique named dual regression analysis (Filippini et al., 2009). Briefly, the individual data in each group were first concatenated along the time direction to find the group level ICA maps. Subsequently, the group level ICA maps were used as the spatial regressors to extract the temporal components from the individual level data. For the data from each individual the corresponding temporal components were then treated as regressors to find subject specific spatial component maps. Lastly, the subject specific component maps for the two age groups were statistically compared by permutation testing, which provides inference about the age association of the TID. The group difference maps were contrast masked (i.e., the group 1 minus group 2 contrast was masked by the group 1 mean contrast), and confidence level was chosen to be 95% (i.e., p < 0.05). The analysis was conducted utilizing the dual regression tool of FSL developed ICA technique named dual regression analysis (Filippini et al., 2009).
To inspect group-wise deactivation strength differences, the registration and ROI extraction of individual data were achieved with FSL FLIRT and fslroi tools, respectively. The ROI data were subsequently processed with custom Matlab (Mathworks, Natick, MA) procedures for correlation filtering, averaging, least mean squares fitting, and statistical testing.

### Results

#### Demographic Information

Data from 76 right-handed normal volunteers, with ages ranging from 4 to 23 years, were evaluated. Forty-five of these (28 from CNMC and 17 from CHOA) passed our motion criteria and were subsequently analyzed. Of these participants, 25 were female and 20 were male. The age of the participants ranged from 5.7 to 21.9 (mean 12.6 ± 4.2) years. The participants were evenly split to two age groups: a young group ($n=23$) with ages ranging from 5.7 to 9.4 years and an old group ($n=22$) with ages ranging from 9.4 to 21.9 years.

#### Table 1
Neuropsychological data and demographic characteristics of the participants.

<table>
<thead>
<tr>
<th></th>
<th>Young group</th>
<th>Old group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td><strong>Age (SD)</strong></td>
<td>9.4 (2.0)</td>
<td>16.0 (2.8)</td>
</tr>
<tr>
<td><strong>Neuropsychology (SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>116 (16.9)</td>
<td>108 (11.9)</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>111 (11.9)</td>
<td>106 (9.9)</td>
</tr>
<tr>
<td>Full scale IQ</td>
<td>115 (14.7)</td>
<td>107 (9.1)</td>
</tr>
</tbody>
</table>

*The neuropsychology scores are based on 21 participants in the young group and 16 participants in the old group.*

![Fig. 1. Task-induced deactivation of the whole participant group ($n=45$) for fMRI paradigms: (a) AUDCAT; (b) ADDT; and (c) Listening. Deactivation was located in the ACC, PCC, mPFC, precuneus, and bilateral parietal lobe. Compared with AUDCAT and ADDT the listening paradigm induced only limited deactivation in mPFC and PCC/precuneus and no deactivation in the parietal cortex regions. Please note that the color display of each parametric map is scaled individually ($Z$ range is [2.3, 6.6] for AUDCAT, [2.3, 6.2] for ADDT and [2.3, 5.9] for Listening).]
11.8 (9.4 ± 2.0), and an old participant group (n = 22) with ages ranging from 12 to 21.9 (16.0 ± 2.8).

Verbal, performance and full-scale IQs (VIQ, PIQ and FSIQ) were collected for 34 of the 45 participants (21 for the younger group and 16 for the elder group). Both the overall and group-wise IQ scores were normal, while the younger group exhibited statistically higher VIQ and FSIQ than the elder group (p = 0.046 and 0.024 for VIQ and FSIQ, respectively). Table 1 lists the demographic and neuropsychological results for the two participant groups.

No signs of age related performance disparity were observed based on the real-time monitoring of participants’ responses to beeps and task questions. Retrospectively, we additionally analyzed the task response accuracy for the ADDT paradigm in 26 participants whose responses were recorded. A linear regression of performance accuracy against participant age was performed and the resulting p value, calculated by applying the Fischer’s transformation on the Pearson correlation coefficient (r), was 0.72.

**GLM analysis**

For the grand mean effect analysis of all participants (n = 45), deactivation areas were identified in typical DMN regions (Fig. 1). Specifically, deactivation was located in the ACC, PCC, mPFC, precuneus, and bilaterally in the occipito-parietal junction. However, there were differences in TID based on task. The extent of deactivation was similar for ADDT (11,218 total number of voxels) and AUDCAT (11,082 voxels) but the deactivation induced by the listening task was significantly weaker (2323 voxels). Compared with AUDCAT and ADDT, the Listening task induced very limited deactivation in mPFC and PCC/precuneus and no deactivation in the parietal cortex regions.

The age effects (positive correlation between age and deactivation) for all three fMRI paradigms are shown in Fig. 2. Age associated consolidation of the TID were present for the AUDCAT and ADDT paradigms but not for the listening paradigm. For the AUDCAT paradigm,
the areas of age associated consolidation were limited to the PCC/precuneus while for the ADDT paradigm the spatial extent of the areas of are related reductions in deactivation was more extensive and included the PCC/precuneus and mPFC.

Similar to the above analysis where age effect is assumed linear, the two-group analysis revealed age associated consolidation of TID (Fig. 3). The younger group consistently showed spatially more extensive TIDs than the old group, regardless of the paradigm. AUDCAT and ADDT induce statistically significant decrease of deactivation in older group in both the PCC/precuneus and mPFC regions (Fig. 3, right panel). For the listening paradigm, no statistical significant decrease of the TID was identified, though a trend is observable (especially in the mPFC) in the mean group contrast images. For all three paradigms, the older group did not show any areas of greater TID than the younger group and the corresponding images are hence not shown.

In contrast, the conjunction analysis revealed numerous regions where stronger deactivation was observed for older participants. The mean and age effects of the deactivation detected by the conjunction analysis are shown in Fig. 4a. The mean deactivation captures the classical DMN cortices as expected. Age is positively correlated with deactivation in the superior temporal gyrus (STG). The group-wise analysis results shown in Fig. 4(b) include both mean contrasts from young and old groups (Fig. 4(b), upper row) and differential

![Fig. 3. AUDCAT (upper row), ADDT (middle row), and listen (lower row) TIDs for young participant (left panel) and old participant (middle panel) groups. The contrast of young minus old is shown in the right hand panel. The young participant group consistently showed spatially more extensive TIDs than the older group, regardless of the paradigm. AUDCAT and ADDT induce statistically significant decrease of deactivation in older participant group (Fig. 3, right panel) in PCC/precuneus and mPFC regions. In the listen paradigm, however, no such decrease of TID reached statistical significance though a trend can be seen, especially in the mPFC, by inspecting the two mean group contrast images.](image-url)
contrasts between the two participant groups (Fig. 4(b), lower row). Consistent with the results in Fig. 4A, for the age dependence of the deactivation, the mean deactivation for the old group is significantly greater than the young group in the STG. On the other hand, the young minus old contrast (Fig. 4(b), lower row left) revealed weaker TID in the older subjects at several DMN cortices. The cortices that exhibit weaker TID in older participants include precuneus and mPFC and are location-wise similar to the results from ADDT and AUDCAT paradigms.

Dual regression analysis of ICA

The numbers of components extracted for AUDCAT, ADDT and listening paradigms in the group-wise ICA analysis were 20, 22 and 24, respectively. The MELODIC tool in FSL estimates the component number based on the covariance matrix of the observations using a Bayesian framework (Beckmann and Smith, 2004). The DMN component was identified based on spatial matching of the component map and DMN locations published in the literature. For all three paradigms, the TIDs are spatially more extensive in the young group than those in the older group through visual inspection (results not shown). The two subtraction contrasts (i.e. Young minus Old and Old minus Young) for the paradigms are shown in Fig. 5. In general, typical DMN regions exhibit more widespread deactivations for one or more fMRI paradigms for the younger group. Specifically, age associated TID reduction was identified in mPFC, PCC/precuneus and parieto-temporal cortex. Such reduction was more pronounced in AUDCAT (Fig. 5, upper row, left), but less so for the ADDT (Fig. 5, upper row, middle) and listening (Fig. 5, upper row, right) paradigms. For AUDCAT, the age association of deactivation contains several separate language areas. Comparatively, age associated increase of TID (Fig. 5, lower row) was limited (for AUDCAT and ADDT) or absent (for listening).

ROI analysis

The two ROIs were selected based on group mean deactivation maps from all three fMRI paradigms. Based on our results, two 40 mm cubic regions were manually selected anteriorly around MNI coordinate (0, 33, 2) to cover TID areas mPFC and ACC, and posteriorly around (0, −59, 32) to cover TID areas PCC and precuneus. A negative relationship is observed between percentage change in deactivation and age in both regions across tasks with the exception of the posterior ROI for the listening paradigm (Fig. 6; Table 2). Table 2 summarizes the $r^2$ and $p$ values for the fitting. It reveals that the trends are statistically significant for the two ROIs in AUDCAT and ADDT but not for the Listening paradigm. With $r^2 = 0.0025$ and $p = 0.7463$, the positive fitting between the deactivation strength and age in the posterior ROI during listening task is likely due to noise.

Fig. 4. (a). The mean and age effects of the induced deactivation by the “combined” language paradigm. The mean deactivation captures the classical DMN cortexes, whereas the age effect appears to be positively correlated with deactivation in the language cortexes (primarily superior temporal gyrus). (b). The young, old, young-old, and old-young contrasts from the group-wise GLM analysis. While the young contrast shows deactivation only in DMN, the old contrast also identifies deactivation in language cortexes. Similar to the result from individual paradigm analysis, the young minus old contrast identified reduced TID in older participants. The old minus young contrast, on the other hand, implies strengthened deactivation in language cortexes (especially superior temporal gyrus) as age increases.

Table 2

<table>
<thead>
<tr>
<th>ROI</th>
<th>$r^2$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUDCAT</td>
<td>0.0025</td>
<td>0.7463</td>
</tr>
<tr>
<td>ADDT</td>
<td>0.0025</td>
<td>0.7463</td>
</tr>
<tr>
<td>Listening</td>
<td>0.0025</td>
<td>0.7463</td>
</tr>
</tbody>
</table>
Comparison of the percentage signal change between the two age groups revealed that the deactivation strength tended to be stronger in the young participants. The $p$ values of the statistical test, with null hypothesis, that the deactivation strength is not higher in the young participant group are listed in Table 2. At the 95% confidence level, the young group shows greater deactivation (strength) in both ROIs during AUDCAT task ($p_b < 0.01$) and in the anterior ROI during the ADDT task ($p = 0.02$).

**Discussion**

In the current study we studied the relationship between age and deactivations induced by language tasks in children and adolescents. Our comprehensive approach utilized three paradigms and multiple complementary analyses. Deactivation occurred within expected DMN regions including ACC, PCC, mPFC, precuneus, and parieto-temporal regions. Results converged across analyses to reveal that with increasing age there was attenuation of TID in terms of both the spatial extent and strength of the TID. However, this age association was confounded by task type. Such task specific modification of the age association of TID has been observed in at least one other study (Park et al., 2010). There was no significant change in performance with age, but there was a non-significant trend towards improved performance with increasing age.

For AUDCAT and ADDT, the GLM and dual regression results convergently identified age associated reduction of TID in the DMN cortices. These findings coincided with the ROI results that older participants have statistically significant reduction of deactivation strength in both posterior and anterior DMN regions for AUDCAT, and the anterior DMN areas for ADDT. Overall, the GLM, ICA and ROI analyses all indicated that the TID decreases from early childhood to adulthood for the AUDCAT and ADDT paradigms. Comparatively, for the Listening paradigm, the GLM analysis did not capture any statically significant age association of TID for both the age contrast (with assumption of linear age association) and the group subtract contrast (with the assumption of piecewise constant age association). Additionally, the ROI analysis also indicated no strength reduction of the deactivation induced by the listening paradigm for the old group compared to the young group. Nevertheless, the dual regression analysis, which also tested the group level difference, did reveal an age associated reduction of TID for the listening paradigm in the DMN cortices. Therefore, for the listening paradigm, the consensus result is that it is less associated with age than the other two paradigms.

Several studies have indicated that the cognitive task load positively correlates with the amount of detectable TID (Esposito et al., 2006; Supekar et al., 2009; Tomasi et al., 2006). This effect is generally explained in terms of lower cognitive loading during easy tasks leading to reduced suppression of default mode activities during the task periods, which, in turn, causes decreased TID as compared to tasks with a high cognitive load. In this study the tasks were selected to give equivalent difficulty across the age range studies and the lack of any significant age effect in the performance data implies that we were reasonably succesful in this aim. Thus the changes in TID that we observed are unlikely to be due to variations in task difficulty. Of the three language paradigms, the listening paradigm is the least demanding because it is a predominantly receptive language task and there was no active decision requirement. This reduced demand to make a semantic decision may explain the largely age independent

![Fig. 5. Group wise comparison of the dual regression analysis for AUDCAT (left panel), ADDT (middle), and listen (right). The upper row highlights regions with age modulated decrease in TID as detected by the ICA analysis, whereas the lower row highlights cortical regions with age modulated increase in TID. DMN regions, including mPFC, PCC/precuneus and parieto-temporal cortex, all exhibited stronger deactivations for the young participant group. Age modulated increase of TID were minimal or undetectable.](image-url)
TID observed for the listening paradigm as there was only minor disruption of DMN connectivity in all ages, and hence there is little variability in the first place. While listening is potentially less demanding semantically, grammatically and syntactically (but possesses greater textual demand), the participants were aware that they would be tested on their recall of the stories after the completion of the scan. This could have "distorted" both the TID and the age association of TID for this paradigm since there is a the memory component which spans the whole paradigm.

The ability to invoke the DMN to a greater degree could be a sign of improved differentiation of cognitive abilities as it indicates higher level skills such as self-monitoring and free associative thought processes (Marsh et al., 2006). The lifespan trajectory of the DMN may follow a similar developmental pattern to most processes whereby there is an increase in engagement/growth in childhood and adolescence, a plateau over adulthood, and then a decrease as the end of life aging occurs. Age related increased DMN synchronization (connectivity) has been detected in children (Fair et al., 2008; Supekar et al., 2010), and aging related decrease in the default mode connectivity is well supported by resting state fMRI studies in adult populations (Damoiseaux et al., 2008; Koch et al., 2010) but different process may well underlie these two trends. In children, the age association of TID is possibly determined by two competing forces: 1) positive relationship between age and DMN connectivity, and 2) negative relationship between age and DMN suppression during active tasks. As the brain matures, there is

Fig. 6. Linear fitting of the percentage signal change and participant age. The anterior ROI contains mPFC, ACC and adjacent DMN cortices and the posterior ROI contains PCC, precuneus and adjacent DMN regions. A negative relationship was observed between percentage deactivation change and age in all cases except for the posterior ROI in the case of the listening paradigm.

Table 2
Linear fitting between percentage signal difference and age, and the two group t-test statistics.a

<table>
<thead>
<tr>
<th></th>
<th>DMN (posterior brain)b</th>
<th>DMN (anterior brain)c</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUDCAT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>$-9.475 \times e^{-5}$</td>
<td>$-7.573 \times e^{-5}$</td>
</tr>
<tr>
<td>$r^2$</td>
<td>0.1431</td>
<td>0.1759</td>
</tr>
<tr>
<td>Correlation $p$</td>
<td>0.0104</td>
<td>0.0041</td>
</tr>
<tr>
<td>Two-group $p$</td>
<td>0.0063</td>
<td>0.0068</td>
</tr>
<tr>
<td><strong>ADDT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>$-5.876 \times e^{-5}$</td>
<td>$-7.666 \times e^{-5}$</td>
</tr>
<tr>
<td>$r^2$</td>
<td>0.0905</td>
<td>0.2249</td>
</tr>
<tr>
<td>Correlation $p$</td>
<td>0.0446</td>
<td>0.0010</td>
</tr>
<tr>
<td>Two-group $p$</td>
<td>0.2177</td>
<td>0.0223</td>
</tr>
<tr>
<td><strong>Listen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>$1.097 \times e^{-5}$</td>
<td>$-3.480 \times e^{-5}$</td>
</tr>
<tr>
<td>$r^2$</td>
<td>0.0025</td>
<td>0.0393</td>
</tr>
<tr>
<td>Correlation $p$</td>
<td>0.7463</td>
<td>0.1918</td>
</tr>
<tr>
<td>Two-group $p$</td>
<td>0.7442</td>
<td>0.1442</td>
</tr>
</tbody>
</table>

a The correlation $p$ was based on a two tailed $t$ test ($n=45$) of the Pearson correlation ($r$); and the two group $p$ was based on testing whether the percentage signal change was significantly greater in the young group than the old group. Statistically significant $p$ values (95%) were italicized.

b The ROI includes all deactivated voxels (correlation coefficient with expected deactivation response>0.1) region center around Talairach coordinate $(x=0, y=-58.9355, z=32.4090)$.

c The ROI includes all deactivated voxels (correlation coefficient with expected deactivation response>0.1) region center around Talairach coordinate $(x=0, y=33.1227, z=2.0271)$. 

TID observed for the listening paradigm as there was only minor disruption of DMN connectivity in all ages, and hence there is little variability in the first place. While listening is potentially less demanding semantically, grammatically and syntactically (but possesses greater textual demand), the participants were aware that they would be tested on their recall of the stories after the completion of the scan. This could have “distorted” both the TID and the age association of TID for this paradigm since there is a the memory component which spans the whole paradigm.

The ability to invoke the DMN to a greater degree could be a sign of improved differentiation of cognitive abilities as it indicates higher level skills such as self-monitoring and free associative thought processes (Marsh et al., 2006). The lifespan trajectory of the DMN may follow a similar developmental pattern to most processes whereby there is an increase in engagement/growth in childhood and adolescence, a plateau over adulthood, and then a decrease as the end of life aging occurs. Age related increased DMN synchronization (connectivity) has been detected in children (Fair et al., 2008; Supekar et al., 2010), and aging related decrease in the default mode connectivity is well supported by resting state fMRI studies in adult populations (Damoiseaux et al., 2008; Koch et al., 2010) but different process may well underlie these two trends. In children, the age association of TID is possibly determined by two competing forces: 1) positive relationship between age and DMN connectivity, and 2) negative relationship between age and DMN suppression during active tasks. As the brain matures, there is
an inherent increase in the DMN connectivity resulting in increased TID. But this is counterbalanced by a reduction in the suppression of the DMN connectivity during active tasks, leading to a decreased TID. The reduced TID seen in more mature brains during active tasks in this study may suggest superior cognitive efficiency (i.e. better “multitasking” resulting in more efficient shifting and allocation of resources in the mature brain). As long as there is sufficient cognitive capacity left to assign to the active task, the mature brain is likely to largely preserve DMN functioning as there would be no benefit from suppressing it. As a separate analysis of the DMN connectivity was not conducted in the current study, it is not possible to determine how the connectivity evolved with age but the results of this study would seem to imply that the age dependent reduction in the suppression of the DMN during an active task predominates over improved connectivity for the AUDCAT and ADDT paradigms. This would also supports the observation of dampened age association of TID for simpler tasks since reduced cognition loading in simple tasks results in weaker DMN suppression during the active tasks. The current findings seem contrary to an earlier study, which observed a positive relationship between age and TID in children (Marsh et al., 2006). However, in that particular study no age adjustments of task difficulty were made, thus the cognitive loading for the same task is likely to differ between younger and older participants. Furthermore, the rest condition in that study involved a congruent task rather than a resting state, which in turn provides different task effects compared to the current study. It should be noted that our paradigms have an element of attention in the rest period (listening for beeps) so the TID may not achieve the same amplitude as it would for a fixation period. As previous study indicated (Lustig et al., 2003), a worse performance could also potentially lead to reduced TID, however, this effect is probably not responsible for the observed age associated reduction of TID in the current study. Specifically, the current study matched the task difficulty level to the IQ scores such that all participants should feel equally challenged by their customized tasks, which should largely eliminated the disparity in task performance. Additionally, the response data indicated no significant trends in age related performance in the studied population.

We also observed a stronger deactivation of the STG in older participants. While the STG has long been considered to play a central role in language processing, anatomical and functional data suggests that it contains mainly auditory cortex and that its role in language relates mainly to the perception of speech and auditory processing (Binder et al., 2009). The literature on the DMN does not typically include the STG and we hypothesize that the age related trend in deactivation may be due to BOLD activation incurred during the rest condition (reverse speech) and is likely unrelated to the DMN. The resting conditions in the paradigms used in this study consist of reverse speech that have no syntax and are semantically meaningless. The recruitment of this region could be due to brain’s effort to “decipher” the reversed speech and this may be more likely to occur in older subjects with more mature language faculties. For individual paradigms, the age effect on this deactivation was not detectable (though the mean contrast from both age groups showed deactivation in this region for AUDCAT). The “combined” analysis, thanks to its improved sensitivity in detecting common patterns shared by all the paradigms, illustrates the age association of this deactivation.

The current study applied dual regression analysis (Filippini et al., 2009) to compare the TIDs of the two age groups. Unlike the GLM analysis, the dual regression analysis makes no assumption about the hemodynamic response function and thus may provide better fitting of the data. Overall, the results from dual regression were comparable to those from the GLM analysis with both approaches showing a general trend towards spatial consolidation of TID in older children. However, distinctions existed in multiple regions. For AUDCAT, the TID regions associated with age are more widespread in the dual regression results. For ADDT, the TID reduction for older children was identified in the PCC and precuneus regions by the GLM but not dual regression analysis. For the listening paradigm, only the dual regression analysis detected age association of TID in the PCC and precuneus regions. Such discrepancies could probably be explained by the different sensitivities of the two approaches in identifying age association of TIDs. Unique to the dual regression analysis, small areas of age associated TID enhancement (brain stem for AUDCAT and oPFC for ADDT) were identified in the older population group. While it is possible that it reflects an age related shift in the location of the DMN, a more likely explanation is that these regions are subject to susceptibility artifacts induced by respiration that varies in a systematic fashion with age.

The current study also performed a ROI analysis of the DMN regions to evaluate the variation in the strength of the deactivation with age. The results showed a general trend of reduced TID strength with increasing age. As mentioned previously, such results may reflect reduced suppression of the DMN connectivity during active tasks (increased multitasking ability) with increasing age. While this trend is less convincing for the listening paradigm, it is consistent with the GLM and dual regression findings. Though it was not the main objective of the current study, we also found signs of age related decreased BOLD activation during task blocks. It is worthy to note that such decreases were also identified in the contra-lateral side of the dominant language hemisphere for the ADDT and listening paradigms, potentially reflecting a more bilateral distribution of language processing in younger children. This observation was reported by a previous study (Szallaszki et al., 2006).

There were several limitations to the current study. First, the number of participants (n = 45) in the current study is limited and the age range of each of the two groups is relatively broad. Further investigations with more subjects are needed to help define factors about the age association of the DMN-functional cortex interaction. Furthermore, the IQ scores between the two age groups are not optimally matched though all participants exhibit IQ scores in normal range. Moreover, the assumptions of both linear and piece-wise constant age association in the studied population are likely oversimplified. Events such as cortical pruning do not occur linearly across the age range covered by this study, which may have distorted the group comparisons. Consequently, the current analyses might not achieve the highest sensitivity in detecting the effect of age association. The MRI data in the current study were acquired at two different sites (CNMC and CHOA) and while efforts were made to standardize the fMRI scanning protocols and no differences in activation patterns were identified in prior study across multiple sites (You et al., 2011), it is possible that this introduced additional confounding factors into our data. Standard motion correction was applied to all data sets and subjects with what was deemed to be excessive motion were excluded. However, it is possible that the type and/or degree of motion varied systematically with age and this may have introduced some bias into the data. No attempt was to include the degree of detected motion as a regressor in the analysis performed for this study, partly due to the difficulty in characterizing the motion but this may warrant further study. Similarly, no physiological data was recorded for these studies but age dependent changes in the respiratory cycle may also have biased the results. For future studies, we aim to record such data and include it in the analysis.

Conclusions

In conclusion, the current study observed an age associated decrease of language task induced deactivation in the DMN in children aging from 5.7 to 21.9 years. We postulate that this could be attributed to the reduced DMN suppression during active language tasks and probably reflects increased cognitive efficiency with increasing age. Additionally, the GLM analysis on the concatenated fMRI data revealed a bilateral age associated increase in deactivation in the STG, implying greater participation of this region when exposed to meaningless auditory stimulation in older participants.
Acknowledgments

This work is supported by the generous support from the American Epilepsy Society, NINDS R01 NS44280, Partnership for Pediatric Research Epilepsy Foundation; Children's Research Institute Avery Award, Intellectual and Developmental Disabilities Research Center at Children's National Medical Center (NIH IDDRC P30HD40677) and the General Clinic Research Center (NIH GCRC M01-R13297). The authors are also thankful for the support provided by the National Science Foundation under grants HRD-0833093, CNS-0959985, and CNS-1042341.

References
