Advanced paternal age effect on offspring’s reading ability: The mediating role of thalamic maturation

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Abstract

While advanced paternal age (APA) has repeatedly been associated with higher risk for neuropsychiatric disorders, its effects on cognitive processes such as reading have received minimal attention. Therefore, we examined the relationship between APA, offspring’s reading abilities, and brain measures in a longitudinal neuroimaging study following 51 children from kindergarten through third grade. APA significantly predicted reduced reading performance, independent of parental reading history, socioeconomic status, home literacy environment, and birth order. This effect was mediated by gray matter volume change in the left posterior thalamus, predominantly the pulvinar nuclei. Complementary analyses using diffusion imaging data, Neurosynth, and 1000 Functional Connectome data indicated the APA-related cluster links to the dorsal attention network. These findings provide novel insights into the neurocognitive mechanisms underlying APA effect on reading during its earliest phase of reading acquisition and suggest future avenues of research on APA-related factors, such as de novo mutation, in reading.

Keywords: Advanced paternal age, brain maturation, diffusion tractography, dyslexia, longitudinal, pulvinar nuclei, reading, thalamus, dorsal attention network, voxel-based morphometry

Abbreviations: APA, advanced paternal age at childbirth; ARHQ, Adult Reading History Questionnaire; DAN, dorsal attention network; DNA, deoxyribonucleic acid; FDR, false discovery rate; FWE, family wise error; MatAGE, maternal age at
childbirth; MNI, Montreal Neurological Institute; MRI, magnetic resonance imaging; PA, phonological awareness; PatAGE, paternal age at childbirth; pIQ, performance intelligence quotient; RAN, rapid automatic naming; RD, reading disorder; READ, reading composite score; ROI, region-of-interest; RSFC, resting-state functional connectivity; SES, socioeconomical status; t1, time-point 1; t2, time-point 2; TIV, total intracranial volume; V5/MT, middle temporal visual area; VAN, ventral attention network; VBM, voxel-based morphometry
Introduction

There has been a global trend of postponed childbearing, especially in developed countries, primarily owing to changing patterns of education, employment and marriage (Bray, Gunnell, & Smith, 2006; Khandwala, Zhang, Lu, & Eisenberg, 2017; Malaspina, Gilman, & Kranz, 2015). Mounting evidence reveals that advanced paternal age at childbirth (APA) increases risk for a wide range of neuropsychiatric conditions in offspring, such as intellectual disability, schizophrenia, autism spectrum disorder, and obsessive-compulsive disorder (Chudal, Leivonen, Rintala, Hinkka-Yli-Salomaki, & Sourander, 2017; D’Onofrio et al., 2014; Reichenberg et al., 2006; Sartorius & Nieschlag, 2010; Weiser et al., 2008).

In comparison to mental health, there is a paucity of research on the influence of APA on offspring’s academic skills such as reading, which are essential for success in the modern society. A pioneering study in 1978 reported a negatively skewed distribution of paternal age at childbirth in a group of forty-eight boys with developmental dyslexia (Jayasekara & Street, 1978). After a thirty-year-long silence on the topic, Saha et al. (2009) demonstrated a negative effect of APA on six neurocognitive assessments including reading in children at age seven. The effect remained significant after controlling for maternal age, child’s gestational age, gender and race (Saha et al., 2009). However, re-analysis of the same dataset questioned the conclusion. Edwards and colleagues found that familial characteristics such as maternal education and family size may account for the
negative APA effect on their child’s cognitive measures since the effect was no longer significant after controlling for these factors (Edwards & Roff, 2010), highlighting the need to consider environmental factors in further studies.

Besides this effect of APA on offspring’s academic abilities remaining an open question, no studies until now have explored potential underlying mechanisms. Nascent research in other fields however has offered some clues at the molecular level. For example, males of advanced age have increased number of cell divisions of the gametes as opposed to females of the same age (approximately 38-fold at the age of 50), leading to a greater rate of paternal \textit{de novo} mutations\footnote{\textit{de novo} mutation is an alteration in a gene that is present for the first time in one family member as the result of a mutation in a germ cell (egg or sperm) of one of the parents or in the fertilized egg itself (https://ghr.nlm.nih.gov/primer/mutationsanddisorders/genemutation).} that doubles every 16.5 years (Crow, 2000). In a genome-wide analysis that examined the parental origin of \textit{de novo} mutations in Icelandic triads, father’s age explained nearly all the variance in the \textit{de novo} mutation counts (Kong et al., 2012). In a separate line of research, \textit{de novo} mutations have been associated with negative mental health outcomes such as higher prevalence of developmental disorders (Deciphering Developmental Disorders Study, 2017; Eising et al., 2018; Kim et al., 2017; O’Roak et al., 2011; O’Roak et al., 2012; Sanders et al., 2015; Turner et al., 2017; Wilfert, Sulovari, Turner, Coe, & Eichler, 2017). Taken together, it is conceivable that \textit{de novo} mutations at least partially mediate the negative effect of APA on offspring’s

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\textit{de novo} mutation is an alteration in a gene that is present for the first time in one family member as the result of a mutation in a germ cell (egg or sperm) of one of the parents or in the fertilized egg itself (https://ghr.nlm.nih.gov/primer/mutationsanddisorders/genemutation).
mental health, and this offers a plausible explanation of the potential APA effects on children’s academic abilities such as reading (Mascheretti et al., 2017).

On the behavioral level, it would be extremely informative to understand whether and how the APA effect is mediated by cognitive-linguistic skills, but this question has never been asked before. Given that de novo mutation is most likely to be the molecular mechanism underlying the APA effect, factors playing a mediating role would be heritable but not necessarily inherited traits. Studies on reading have examined phonological processing most extensively, and found it to be influenced by genetics, environment, as well as brain anomalies (Mascheretti et al., 2014; Mirman et al., 2015; Petrill, Deater-Deckard, Thompson, DeThorne, & Schatschneider, 2006), making it a candidate trait to be testified. Specifically, phonological awareness (PA) and rapid automatized naming (RAN), the most critical processes in reading acquisition, is of particular interest to the current study (Hulme, Snowling, Caravolas, & Carroll, 2005; van Bergen, Bishop, van Zuijen, & de Jong, 2015). At the brain level, despite emerging evidence suggesting that neural processes measured by neuroimaging techniques (e.g., magnetic resonance imaging; MRI) may serve as mediators between genetic etiology and behavioral outcome thereby acting as endophenotypes, such approaches have yet to be utilized in the examination of APA effects on neuropsychiatric disorders and neuro-cognitive skills (e.g., Bas-Hoogendam et al., 2016; Spencer et al., 2012).

Therefore, we aimed to close the gap in the literature by: (1) examining the relationship between APA and offspring’s reading abilities while controlling for a
number of factors that potentially impact APA and/or offspring’s reading in a systematic way; (2) exploring the role of previously known reading precursors and neuroanatomy in the relationship between APA and reading; and (3) understanding the neurofunctional significance of the findings by utilizing atlases and public datasets as well as by conducting complementary multimodal imaging analyses. To accomplish these goals, we examined behavioral and neuroimaging data both cross-sectionally and longitudinally in a study following 51 children from kindergarten through third grade.

Results

APA is associated with poor reading above and beyond commonly known predictors

The distribution of paternal age at childbirth (PatAGE; Mean = 36.12 years, SD = 4.91; Table S1) is presented in Figure 1A. Simple correlation analyses revealed that as expected, PatAGE was significantly and positively correlated with maternal age (MatAGE; r = 0.63, p < 0.001; Table S2). PatAGE was positively correlated with maternal history of reading difficulty, measured by Adult Reading History Questionnaire (MatARHQ; r = 0.34, p = 0.028), i.e., older age of fathers was correlated with poorer reading history of mothers. On the contrary, there was no significant correlation between PatAGE and paternal history of reading difficulty (r = -0.011, p > 0.1). Importantly, we found greater PatAGE significantly correlated with lower reading composite scores in offspring at third grade (time-point 2;
t2READ; \( r = -0.39, p = 0.011 \). No significant correlations were found at either time-point between PatAGE and cognitive-linguistic skills typically found to be predictors of later reading ability, such as PA and RAN (\( p \)'s > 0.1 for time-point 1 PA composite score at kindergarten \([t1PA]\), RAN composite score \([t1RAN]\), \( t2PA \), and \( t2RAN \)). In accordance with prior literature on factors that predict reading outcomes, poorer \( t2READ \) was predicted by poorer cognitive-linguistic skills at time-point 1 (\( t1PA: r = 0.46, p = 0.002 \); \( t1RAN: r = 0.31; p = 0.041 \)), greater MatARHQ \( (r = -0.46, p = 0.002) \), and poorer home literacy environment measured by Home Observation Measurement of the Environment (HOME: \( r = 0.31, p = 0.047 \)) (Segers, Damhuis, van de Sande, & Verhoeven, 2016; Thompson et al., 2015; van Bergen et al., 2015). Furthermore, MatAGE was negatively correlated with \( t2READ \) \( (r = -0.33, p = 0.031) \), similar to PatAGE.

To examine whether the APA effect on reading existed above and beyond commonly identified confounds and additional variables known to influence reading acquisition, hierarchical multiple linear regressions were conducted with \( t2READ \) as the dependent variable in a systematic and hypothesis-driven fashion. In the first model, before PatAGE was entered in the second step, confounding factors related to the child were entered as predictors in the first step, including \( t2 \) age, gender, handedness and the mean average of performance intelligence quotient \( (\text{pIQ}) \) at the two time-points (to produce more stable estimates of pIQ; measured by Concept Formation sub-test from Woodcock-Johnson III Test of Cognitive Abilities). We found that the PatAGE effect remained significant, explaining 14.9% of
additional variance ($\Delta R^2 = 0.149$, $t = -3.115$, $p = 0.004$; Model 1 in Table 1). In the second model, while the variables in the first step stayed the same, familial measures were entered in the second step, including maternal age, socioeconomic status (SES), maternal reading history and paternal reading history, before PatAGE was entered in the third step. As the results showed, PatAGE still explained an additional 9.5% of the variance in reading outcomes ($\Delta R^2 = 0.095$, $t = -2.42$, $p = 0.024$; Model 2 in Table 1). Thus far, we demonstrated the APA effect on reading was not accounted for by confounds related to child or family. In the third model, we went on to investigate its relationship with early cognitive-linguistic skills. With the first two steps remained the same as the second model, we entered $t_1$ cognitive-linguistic skills (i.e., $t_1PA$ and $t_1RAN$) in the third step before entering PatAGE in the fourth step, and the APA effect on offspring’s reading was still above and beyond that of these cognitive-linguistic variables, explaining an additional 7.3% of the variance ($\Delta R^2 = 0.073$; $t = -2.42$, $p = 0.024$; Model 3 in Table 1). Furthermore, in accord with the prior literature, $t_1PA$ and $t_1RAN$ again significantly accounted for $t_2READ$ variance in the final model ($\Delta R^2 = 0.138$; $t_1PA$: $t = 2.83$, $p = 0.010$; $t_1RAN$: $t = 2.14$, $p = 0.043$). In other words, the contributions from PatAGE and cognitive-linguistic precursors were relatively independent.

**APA is associated with neuroanatomical maturation in the left thalamus**

We examined the relationship between PatAGE and global measures of neuroanatomy, i.e., total intracranial volume (TIV) at $t_1$ and $t_2$, as well as change of TIV ($\Delta TIV$, i.e., $t_2TIV-t_1TIV$) between the two time-points, before examining the
relationship between APA and regional brain morphometry. No significant
correlations were observed (all $p$’s > 0.1). Further, whole brain analyses of regional
gray matter volume (GMV) at either time-point showed no significant clusters at $p$
< 0.05 corrected for Family Wise Error (FWE). Lastly, we examined the APA effect
on regional GMV change ($\Delta$GMV, i.e., $t_2$GMV-$t_1$GMV) while controlling for $t_1$TIV
and $\Delta$TIV. Results revealed a significantly positive correlation between PatAGE and
$\Delta$GMV in a cluster covering the left posterior thalamus (hereafter APA-cluster; $p =$
0.017, FWE corrected, 819 voxels, peak MNI coordinate [-27, -30, 6]; Figure 2A).
Specifically, greater paternal age was associated with less GMV decrease in this
cohort (Figure 2B). To verify that this APA effect was not due to confounding
variables, hierarchical multiple regression analyses were performed. In the first
model, after regressing out nuisance variables commonly controlled in longitudinal
VBM studies ($t_1$ age, time interval between $t_1$ and $t_2$, gender, handedness, average
pIQ of $t_1$ and $t_2$, $t_1$TIV and $\Delta$TIV), PatAGE still explained 34.6% of the variance in
average $\Delta$GMV of the APA-cluster ($t = 4.59, p < 0.001$). Since MatARHQ and
MatAGE were significantly correlated with PatAGE, we additionally regressed
them out in the second model. We found that PatAGE still explained 19.0% of the
variance in average $\Delta$GMV of the APA-cluster ($t = 3.28, p = 0.003$).

APA effect on offspring’s reading is mediated by $\Delta$GMV in the left posterior
thalamus

To further examine whether $\Delta$GMV in the APA-cluster was correlated with reading,
we performed voxel-wise regression within this cluster while controlling for $t_1$TIV
and ΔTIV. As shown in Figure 2, there was a negative correlation between ΔGMV and $t_2$READ in a sub-region of the APA-cluster ($p$-cluster = 0.037, small volume FWE corrected, 86 voxels, peak MNI coordinate [-27, -31, 10]), indicating that the poorer the reading skill, the less the thalamic GMV decrease between the two time-points. Hierarchical multiple regression analyses were performed to verify the result. We found that ΔGMV of the significant cluster explained 19.7% of variance in $t_2$READ after regressing out nuisance variables ($t_2$ age, gender, handedness, average pIQ, $t_1$TIV and ΔTIV) in the first step ($t = -3.20, p = 0.003$). Since $t_2$READ was also significantly correlated with the two cognitive-linguistic skills $t_1$PA and $t_1$RAN, we examined whether the observed effect was above and beyond cognitive-linguistic skills by entering these two measures in the second step. The results showed that ΔGMV additionally explained 19.9% of the variance in $t_2$READ ($t = -3.66, p = 0.001$).

Given that ΔGMV in the left thalamic sub-region was significantly associated with both PatAGE and $t_2$READ, one possibility is that ΔGMV mediates the APA effect on offspring’s reading. To test this hypothesis, we ran mediation analysis and observed a significant mediation effect. The 95% confidence interval was [-0.522 - 0.041] when not controlling for age at $t_2$, gender, handedness, average of $t_1$ and $t_2$ pIQ, TIV at $t_1$, TIV change from $t_1$ to $t_2$, $t_1$PA, and $t_1$RAN; the 95% confidence interval was [-0.552 - 0.043] when these covariates were controlled (Figure 3). In supplementary materials, this result was discussed in relation to an additional finding that early PA skills mediated the effect of maternal reading history on
reading outcome (95% confidential interval was [-0.303, -0.022] when not controlling for age at t2, handedness, average of t1 and t2 pIQ, and t1RAN, and changed to [-0.249, -0.001] when these covariates were controlled; Figure S1).

The APA-cluster is localized in the pulvinar nuclei and highly linked to the dorsal attention network

To understand the neurostructural profile of the APA-cluster in the left thalamus, we compared the cluster with a histological atlas and a connectivity atlas. The result revealed that 548 out of 819 voxels in the APA-cluster overlapped with the human thalamus of the Morel histological atlas (Jakab, Blanc, Berényi, & Székely, 2012; Krauth et al., 2010), while the remaining 271 voxels could not be labeled, possibly because the APA-cluster also contained white matter. As presented in Figure 4A, within the overlapping region, 380 voxels (69.5%) were in the subdivision labeled as pulvinar nuclei, especially the medial portion, which is known to have widespread connections with the inferior parietal lobule (Arcaro, Pinsk, & Kastner, 2015). These results were further corroborated by examining the Thalamic Connectivity Probability Atlas (http://fsl.fmrib.ox.ac.uk/fsl/fslview/atlas.html), where we found that the APA-cluster was most likely localized in the subdivision that was connected to the posterior parietal cortex, with a probability of 38.9% (Figure 4B).

We next examined functional connectivity of the APA-cluster by utilizing two approaches available in Neurosynth (v0.5; Yarkoni, Poldrack, Nichols, Van Essen,
& Wager, 2011). These included generation of a meta-analytic map of regions that co-activate with the APA-cluster across more than 10,900 functional MRI (fMRI) studies, as well as a resting-state functional connectivity (RSFC) map from the APA-cluster using the 1000 Functional Connectome dataset (Biswal et al., 2010; Yeo et al., 2011). The co-activated areas included subcortical structures and cortical regions such as bilateral intraparietal sulci, inferior temporal gyrus, and frontal eye fields in the frontal cortex (Figure S2A). On the other hand, functional connectivity patterns showed similar but more widespread networks than the co-activation map (Figure S2B). A conjunction analysis revealed that bilateral frontal eye fields, intraparietal sulci, middle temporal visual area (V5/MT), and cerebellum were among the overlapped regions across the two approaches, in addition to subcortical structures (Figure 5A).

We then calculated Sørensen-Dice coefficient \( (s) \) between the overlapping areas and previously identified functional networks during resting state (Yeo et al., 2011). The derived pattern of overlapping areas showed the greatest resemblance to the dorsal attention network (DAN; \( s = 0.360 \); Figure 5B) and to the ventral attention network (VAN; \( s = 0.261 \)), much higher than its resemblance to other networks (visual network: \( s = 0.086 \); somatomotor network: \( s = 0.071 \); limbic network: \( s < 0.001 \); frontoparietal network: \( s = 0.041 \); and default network: \( s = 0.005 \)). Together with the aforementioned findings utilizing structural atlases, these results using large-scale fMRI databases from functional neuroimaging studies...
point to the attention network, in particular the DAN, to be the candidate brain functional system associated with the APA-cluster in the left thalamus.

In the final step, we used diffusion imaging data available in a sub-group of 23 participants to determine which was more likely the candidate. Using deterministic tractography, we reconstructed white matter fibers through the APA-cluster, covering inferior fronto-occipital fasciculus, corticospinal tract, forceps major, superior corona radiata, as well as anterior and posterior limbs of the internal capsule. Figure 6A shows reconstructed fibers in a representative child and Figure 6B shows intersection across participants, for demonstrative purposes. More importantly, the APA-cluster showed significantly stronger connectivity (defined by dividing the total number of streamlines by the size of the target network) with DAN than with VAN ($t = 6.61, p < 0.001$; Figure 6C). Finally, consistent with the aforementioned results, correlation analyses showed significant positive correlation between APA-DAN streamlines and PatAGE ($r = 0.49, p = 0.018$; Figure 6D), and significant negative correlation between APA-DAN streamlines and $t^2$READ ($r = -0.45, p = 0.030$; Figure 6E). No significant correlations were found between APA-VAN streamlines and PatAGE or $t^2$READ (both $p's > 0.1$).

**Discussion**

The present study provides evidence that APA is negatively associated with offspring’s reading by rigorously controlling for a number of potential confounding factors and for the first time investigates neurocognitive mechanisms underlying
the APA effect on reading by using multiple neuroimaging modalities and online databases/atlas. We showed that the APA effect on reading skills was independent of familial factors such as parental reading history, SES (an aggregate measure of family income, parental educational level and occupation), and home literacy environment. We also investigated the neurobiological correlates of APA, identifying it to be the grey matter development in the left thalamus. The association between paternal age and reading was mediated by morphometric changes of the left posterior thalamus when examined at the earliest stages of formal schooling from ages 5 to 8. With the aid of multimodal neuroimaging, we identified this region in the left thalamus as most relevant for dorsal attention network. These findings are in contrast to and complement the literature linking phonological and orthographic processing in reading to the left temporo-parietal and occipito-temporal regions. Furthermore, the mediation relationship revealed here was different from the mediating effect of phonological processing on the relationship between reading and maternal reading history, which has been attributed to hereditary effects (van Bergen et al., 2015). Together, we provided converging evidence that APA may be a risk factor that negatively impacts reading, independent of phonological processing, through an altered maturational process of the left thalamus.

Potential mechanisms of APA effect on offspring’s reading

In this study, we demonstrated a negative APA effect on offspring’s reading abilities. This finding is consistent with a study in boys with dyslexia (Jayasekara & Street,
1978) and a more recent population-based study (Saha et al., 2009). As shown by
Jayasekara and Street (1978), APA was associated with greater incidence of
developmental dyslexia, independent of SES and birth order. While the former
study was restricted to a small number of boys with dyslexia, Saha et al. (2009)
extended the finding to a broader population. By conducting population-based
analyses, the authors observed negative APA effects on several neurocognitive
measures that included reading. The effects remained significant after controlling
for confounding factors such as mother’s age, SES, and parental psychiatric illness.
It should be noted that the relationship was nonlinear, which might be caused by
the fact that fathers of extreme young as well as old ages were included in their
analyses (range of paternal age was from 14 to 66 years). When focusing on the
range of paternal age examined in our study (i.e., 25-47 years), a linear decrease in
reading scores with increasing paternal age was observed (Saha et al., 2009).
However, the effect observed in the earlier studies could be confounded partially by
familial characteristics. For example, Edwards and Roff (2010) found the APA effect
on reading to be no longer significant after adjusting for confounding factors such as
maternal education and family size, highlighting the need for more comprehensive
and rigorous studies before deriving the conclusion that APA negatively affects
reading. Against this background, we examined the negative APA effect on reading
by additionally controlling for familial risk for dyslexia (parental reading history)
(van Bergen et al., 2015), home literacy environment (Grigorenko, 2001; S.
Mascheretti et al., 2013), and SES (composite of parents’ educational level,
occupation, and family income). Furthermore, we used a battery of measures to
accurately assess children’s reading abilities after three years of formal reading
instruction. We also acquired cognitive-linguistic precursors of reading (i.e., PA,
RAN, letter knowledge) of these children at the beginning of formal reading
instruction in kindergarten, allowing us to examine reading development
longitudinally. Our results first provide a unique picture of the negative APA effect
on reading, after controlling for possible confounds. Moreover, although there is a
possibility that fathers who are poorer reader may have children later because for
example, they may take time to be financially independent and hence likely have
poor reading children, it is not the case in the current study since we did not find a
significant correlation between PatAGE and paternal ARHQ. This pattern further
confirms the negative influence of APA on reading. Relevant to these findings, we
did not observe associations between paternal age and cognitive-linguistic skills (i.e.,
PA, RAN, letter knowledge) known to be strong predictors of early reading
acquisition, suggesting that paternal age may impact reading through a different
pathway (Hulme et al., 2005; Swagerman et al., 2017; van Bergen et al., 2015).

Mechanisms underlying these APA effects are likely to be complex, involving
genetic, epigenetic and environmental factors. While the number of studies that
examined the APA effect on reading is far too few to allow for a comprehensive
interpretation, studies on other APA-linked neurodevelopmental disorders offer
important insights into potential mechanisms. One predominant explanation is that
APA exerts its effect on the risk of a given disorder through the accumulated de
novo genetic mutations and epigenetic modifications (e.g., DNA methylation and repressive histone modification) in paternal gametes (Girard et al., 2016; Janecka et al., 2017; Kim et al., 2017; Perrin, Brown, & Malaspina, 2007). For example, men who delay fatherhood have an increased number of de novo mutations (e.g., de novo single nucleotide variations) in their sperms and this might proportionally increase the chance of their offspring to carry deleterious mutations that increase risks for certain neurodevelopmental disorders. In line with this explanation, both higher rate of de novo mutations and increased paternal age have been identified in individuals with psychiatric conditions including intellectual disability (Reijnders et al., 2016; Saha et al., 2009), autism (Frans et al., 2013; Sebat et al., 2007), attention deficit hyperactivity disorder (Kim et al., 2017) and schizophrenia (Awadalla et al., 2010; Malaspina et al., 2001; Singh et al., 2016). From another perspective, understanding of mechanisms underlying the APA effect can be deepened by identifying intermediate (endo)phenotypes, which can be observed at the behavioral level or via neuroimaging. In other words, APA may be associated with higher occurrence of neurodevelopmental disorders in offspring through increasing the risk for developing specific precursors of certain disorders (Cannon, 2009). For example, the likelihood of having impaired social functioning in an offspring, which is a core symptom of psychiatric disorders, increases with paternal age (Weiser et al., 2008).

The two types of evidences are at different explanatory levels and corresponding evidences can be combined together to draw a more comprehensive picture.

Although mechanisms underlying the APA effect are not fully understood, the risk
for neurodevelopmental disorders is most likely multidimensional and involve multiple processes including both \textit{de novo} mutations and inherited risks. Adding to prior research, findings of the current study offer insights into potential neural mechanisms at the macroscopic level. We discuss this point further in the following section.

The research on the role of genetics in reading development and disorder is growing. However, while most researchers have focused on examining heritability in twin studies or identifying risk genes for reading disorder (RD) by analyzing single nucleotide polymorphisms (Mascheretti et al., 2017), less attention has been paid to the role of spontaneous mutations and their sources (for exceptions, see Eising et al., 2018; Veerappa, Saldanha, Padakannaya, & Ramachandra, 2013). Based on our findings and studies of the molecular mechanisms of APA where \textit{de novo} mutations were almost exclusively explained by APA (Kong et al., 2012), we propose that \textit{de novo} mutations may be one mediator of APA effects on reading, and a potential risk factor for poor reading. Future research analyzing deoxyribonucleic acid (DNA) from triads exploring the relationship between \textit{de novo} mutations and offspring’s reading phenotypes is warranted. Of relevance, a recent study used whole-genome sequencing in parent-child trios and discovered \textit{de novo} mutations that disrupted specific genes (e.g., \textit{CHD3}, \textit{SETD1A}, \textit{WDR5}) in individuals with childhood apraxia of speech, another common neurodevelopmental disorder (Eising et al., 2018). Similar studies may be a promising approach to reading research.
The left posterior thalamus plays an intermediary role in the APA effect on offspring’s reading

The current study demonstrated a negative APA effect on offspring’s reading after controlling potential confounding factors. It further revealed that this effect was mediated by morphometric maturation of the left posterior thalamus, providing a potential neural explanation at the macroscopic level.

The thalamus is an important relay center in the human brain, connecting cortical and subcortical areas, receiving information from sensory cortices and relaying it to higher-level association areas. Studies in normal populations with cross-sectional designs have produced a mixed picture of the normal developmental trajectory of the thalamus: while the relative gross volume of the thalamus (normalized by brain size) was found to decrease from 4 to 18 years of age by Sussman, Leung, Chakravarty, Lerch, and Taylor (2016), an opposite pattern has also been reported (Brain Development Cooperative, 2012). Such inconsistency could be caused by subnuclei-specific developmental trajectories. In a recent longitudinal study, Raznahan and colleagues demonstrated that while most thalamic nuclei showing age-related areal expansion, regions related to ventral anterior, rostral ventrolateral, and mediodorsal nuclei show contraction. The pulvinar did not show apparent correlations with age (Raznahan et al., 2014). Despite the insufficient evidence on typical thalamic maturation, there is no doubt that anomalous development of the thalamus can severely affect maturation of other cortical and subcortical brain regions (Ball et al., 2012), which may in turn
impact higher level cognitive processes such as reading. In line with this view, structure (Brown et al., 2001; Galaburda & Eidelberg, 1982; Giraldo-Chica, Hegarty, & Schneider, 2015), activation (Brunswick, McCrory, Price, Frith, & Frith, 1999; Diaz, Hintz, Kiebel, & von Kriegstein, 2012; Maisog, Einbinder, Flowers, Turkeltaub, & Eden, 2008; Preston et al., 2010; Pugh et al., 2013), and connectivity (Davis et al., 2010; Fan, Davis, Anderson, & Cutting, 2014; Lebel et al., 2013) of the thalamus have been demonstrated to be associated with individual differences in reading performance (see Goswami, 2015 for a review). In the current study, the volumetric change in the posterior thalamus from ages 5-8 was significantly associated with paternal age. While children with relatively younger fathers showed GMV decrease in the APA-cluster from 5 to 8 years of age, those with older fathers showed less decrease or even an increase. This pattern suggested that APA altered developmental trajectory of this subcortical structure.

Moreover, comparing the APA-cluster with the Morel atlas revealed that the maximal overlap was in the left pulvinar, which plays an integral role in the functioning of the visual cortex (Bridge, Leopold, & Bourne, 2016; Purushothaman, Marion, Li, & Casagrande, 2012). This structure is an integral region for visual processes including visuo-spatial attention (Fischer & Whitney, 2012), motion perception (Shimono, Mano, & Niki, 2012), and visuo-motor transformations (Arend et al., 2008; Shipp, 2004). A recent meta-analytic study on task-based fMRI demonstrated a close relationship between pulvinar and attentional control (Barron, Eickhoff, Clos, & Fox, 2015), which was further supported by another fMRI study.
examining the interaction between three major components of attention (altering, orienting, and executive control) (Xuan et al., 2016). The pulvinar is also involved in writing, which is related to reading and imposes a high demand of visuo-spatial attention among other processes (Yuan & Brown, 2015). Consistent with this line of literature, our results from a deterministic tractography-based thalamo-cortical connectivity atlas showed that this region was most likely connected with posterior parietal areas. Public RSFC and co-activation maps also revealed connections between the APA-cluster and key nodes (e.g., frontal and parietal eye fields) in the attention networks, especially the DAN (Corbetta, Patel, & Shulman, 2008). Additionally, the pulvinar connects to visual motion-sensitive cortices (V5/MT) (Shimono et al., 2012), further indicating that the APA-cluster may be associated with processes related to visuo-spatial attention (Amso & Scerif, 2015; Wu et al., 2015; Wu et al., 2016). The anatomical connectivity between the APA cluster and DAN was confirmed by analyses of white matter diffusion data available in a subset of our sample. Specifically, the APA-cluster showed greater connectivity to DAN than to VAN, and only the connectivity between the APA-cluster and DAN was correlated with both paternal age and children’s reading performance. Together, these findings indicate that the pulvinar and brain networks underlying visuo-spatial attention are parsimonious neurocognitive mechanisms impacted by APA, and their atypical pattern and development may further impede reading acquisition.

To date, research into the APA effect on neural networks and cognitive processes is scarce. The study conducted by Shaw and colleagues focused on
parental age effects on cortical thickness and surface area but did not examine their relationship to cognitive functions, making this study somewhat inconclusive as to the role of parental age on neurocognitive processes (Shaw et al., 2012). Taking one step further, our study revealed an intermediary between paternal age and a specific behavioral phenotype at the neural level, offering initial insights into the complex mechanisms underlying APA effects.

APA as a risk factor for poor reading

Our findings of the APA effect on offspring’s reading also offer insights into the etiologies of RD. Overall, 7% of school-aged children develop RD, characterized by unexpected problems in reading and spelling (Peterson & Pennington, 2012). Although RD has been demonstrated to be heritable (Grigorenko, 2004; Hawke, Wadsworth, & DeFries, 2006), the etiologies are complex and remain largely unknown (Poelmans, Buitelaar, Pauls, & Franke, 2011). For a deeper and more comprehensive understanding, it is essential to examine multiple components of reading and the underlying neural circuitries systematically (Wandell & Le, 2017). Genetic risk has been proposed to impair brain networks underlying auditory and phonological processing, consequently impeding on individual’s reading development (Giraud & Ramus, 2013). But here we demonstrate a unique APA effect on offspring’s reading abilities, independent of parental reading history that is considered to be associated with inherited genetic risk for developing RD (Figure 7) (Hulme et al., 2005; Swagerman et al., 2017; van Bergen et al., 2015). Additionally, this effect appeared to be independent of environmental risks such as
SES and home literacy environment. Our findings are thus in line with an emerging view that RD is associated with accumulative risk from genetics, environments, and their interactions (Bishop, 2015) in both children and adults with RD (Olulade, Napoliello, & Eden, 2013; Shaywitz & Shaywitz, 2008).

The relationship between visuo-spatial attention and reading has been demonstrated consistently and repeatedly by several lines of research. Specifically, impaired visuo-spatial processing has been shown to negatively impact reading acquisition by affecting one’s ability to focus their attention on target symbol-sound correspondences and/or to suppress non-targets (Franceschini, Gori, Ruffino, Pedrolli, & Facoetti, 2012; Shaywitz & Shaywitz, 2008; Vidyasagar & Pammer, 2010). For example, selective visual attention has been associated with acquisition of orthographic knowledge (Bosse, 2015; Stevens & Bavelier, 2012) and decoding skill (Matthews & Martin, 2015). Besides, both adults and children with RD show visuo-spatial attention deficits such as having lower visuo-spatial span capacities and being slower in a visuo-spatial attention-orienting task (Abbott, Larkin, & Dunn, 2015; Bosse, Tainturier, & Valdois, 2007; Judy Buchholz & Davies, 2005; J. Buchholz & Davies, 2008; A. Facoetti, Paganoni, Turatto, Marzola, & Mascetti, 2000; Andrea Facoetti et al., 2006; Roach & Hogben, 2004; Ruffino, Gori, Boccardi, Molteni, & Facoetti, 2014). Third, longitudinal research has demonstrated that impaired visuo-spatial processing in pre-reading kindergarteners is an important risk factor for future reading difficulties (Franceschini et al., 2012; Gori & Facoetti, 2015).
The causal role of impaired visuo-spatial attention in reading difficulty is however, under debate (Gori & Facetti, 2015; Joo, Donnelly, & Yeatman, 2017; Olulade et al., 2013; Vidyasagar & Pammer, 2010). While behavioral evidence supports a causal role of visual deficits in RD (Gori & Facetti, 2015), Olulade and colleagues found that hypoactivation in motion perception related V5/MT in RD existed only when compared with age-matched but not with reading-matched controls, suggesting that this anomaly is driven by impoverished reading experience rather than causally related to RD (Olulade et al., 2013). Given the high association between APA and de novo mutations, our research may shed light on this debate favoring the causal effect of visuo-spatial attention on reading ability. In particular, our results suggest that APA might contribute to lower reading performance via impacting the developmental trajectory of a sub-region of the left thalamus, which connected with dorsal and ventral attentional networks that are important for typical reading development (Da Silva, Ueki, Oliveira, Boggio, & Macedo, 2016). Moreover, integrity of structural connectivity between the APA-related thalamic area with the DAN was significantly correlated with APA as well as reading ability. These results collectively support a possible pathway from APA (possibly via genetic variations), through neurocognitive endophenotypes (left thalamus, possibly related to visuo-spatial attention), to downstream effects on behavior (reading).

It should be noted that our findings do not exclude the possibility that reading experience could also shape visual attention and corresponding neural circuits (Skeide et al., 2017). Neither does this study deny the essential role of
phonological processing in reading development. Instead, our results supported its significance by showing a significant contribution of cognitive-linguistic precursors (PA, letter knowledge, and rapid naming) in addition to APA effect in reading outcomes. Reading is multi-faceted, and dysfunction in any requisite cognitive process could increase the risk of reading difficulties in a probabilistic way (Carroll, Solity, & Shapiro, 2015; Peterson & Pennington, 2012). Correspondingly, it is now widely accepted that RD is an outcome of multiple factors/deficits and the complex interplay among them (Mascheretti et al., 2013; Pennington, 2006). Such Multiple Deficit Model of RD has recently been expanded by introducing parental influences through genetic and cultural transmission known as the Intergenerational Multiple Deficit Model (van Bergen, van der Leij, & de Jong, 2014). Based on our findings, we propose that variables beyond parental genotypes and behavioral phenotypes, such as intermediate neural measures and de novo mutation due to APA, should be added to achieve a more comprehensive understanding of the parental influence on offspring’s reading.

Limitations

In the present study, we found a negative effect of APA on offspring’s reading achievement. However, the results should be interpreted with cautions. First, because the range of paternal age at the time of child’s birth in this study was restricted to 25-47 years, the findings may not necessarily be extended to children with fathers on extreme ends, young or old. Of relevance, young fatherhood has also been associated with adverse cognitive development of the offspring (Weiser et al.,
RUNNING HEAD: THALAMUS LINKS PATERNAL AGE AND OFFSPRING'S READING

2008) but possibly due to different factors such as immature sperm and economic
disadvantages (Chen et al., 2008). Second, because children’s reading abilities were
measured at grade 3, it is unknown whether the APA effect on reading will persist
into adulthood or is simply a developmental delay. Third, since reading performance
of the participants were within typical range, our results show that individual
differences in reading ability are associated with age of the fathers, rather than
direct evidence that late fatherhood is associated with RD in their offspring. Finally,
while we revealed the left posterior thalamus mediated the APA effect on reading,
we could not answer why APA (or de novo mutations) specifically impacts this
subcortical area. Given that the typical maturation of thalamus can be also affected
by prenatal and postnatal factors such as preterm birth (Ball et al., 2012), questions
such as how APA influences maturation of thalamus and relevant functional
systems, together with other factors, require further elaboration.

Conclusion

The current study, for the first time, examined the association between APA and
reading at both a behavioral and neurobiological level. We provided evidence that
APA is an independent factor associated with lower reading ability. We also found
that the APA effect on reading was mediated by maturation of the thalamus. This
suggests a novel neurobiological pathway for intergenerational influence on reading,
completing prior findings that offspring’s reading is influenced by parental reading
via (offspring’s) phonological skills (van Bergen et al., 2015; Vandermosten, Cuynen,
Vanderauwera, Wouters, & Ghesquiere, 2017). Based on these evidences we argued
that APA should be regarded as one significant risk factor for children’s literacy development, and be taken into consideration in the examination of the etiology of RD. To replicate these findings and advance our understanding of this APA effect on reading, future studies are warranted where a more comprehensive battery of behavioral tests that includes visuo-spatial and attentional processes, corresponding neural measures, and molecular approaches that measure the number and origins of de novo mutations (trio-based whole-genome/exome sequencing; Jin et al., 2017), are included. We also hope this study will stimulate future research aiming to address different sources of genetic variations associated with reading development to understand the interplay between genetics and other factors that impact reading development (Pennington, 2006; van Bergen et al., 2014). In particular, further studies could adopt advanced research designs such as intergenerational neuroimaging approach to gain in-depth knowledge on how multiple factors (e.g., paternal age, familial risk, home literacy environment) affect the development of offspring’s reading and the corresponding networks interactively from preliteracy to mature stages of reading (Ho, Sanders, Gotlib, & Hoeft, 2016; Hoeft & Hancock, 2017).

Methods

Participants

Participants were drawn from a longitudinal NIH-funded project (K23HD054720) that focused on children’s reading development from kindergarten (mean age at t1 =
5.58 years, standard deviation [SD] = 0.43) to third grade (partial data from this larger project were included in prior publications unrelated to the goals of the current study: Black et al., 2012; Gimenez et al., 2014; Hosseini et al., 2013; Myers et al., 2014; Yamagata et al., 2016). All children were healthy native English speakers without any neurological or psychiatric disorders (e.g., attention deficit/hyperactivity disorder) or contraindications to MRI based on parental report. Initially, 51 children and their parents were included. For the longitudinal behavior analyses, eight children were excluded because of attrition (n = 5), no record of father's age (n = 1), or more than one child from the same parents (n = 2). In the latter case, we excluded one child from each pair according to T1 image quality, which was qualitatively evaluated by an investigator who was otherwise blind to the behavioral and demographic information. The final sample included 43 unrelated children. For the neuroanatomical analysis, another seven children were excluded because of incomplete T1 data collection or poor image quality at either t1 or t2 by visual check, leaving 36 children in the final sample. For the diffusion-weighted imaging analysis, 23 children with the same acquisition sequence were included. There was no significant difference in either familial or any behavioral measures between the total cohort and any sub-groups (all p’s > 0.1). The Institutional Review Boards of Stanford University where data were collected and principal investigator was at the time of the study, and the University of California San Francisco where data were analyzed due to transition of the principal
investigator, approved the present study. Both informed assent and consent were obtained from children and their parents/guardians.

**Family information and behavioral measurements**

Demographic information, family and behavioral measures are summarized in Table S1. Family information collected at \( t_1 \) include: PatAGE; MatAGE; ARHQ (Lefly & Pennington, 2000) from both parents that was used to estimate familial history of reading difficulty; SES, which was a composite index computed from family annual income, parental educational level and occupation with principal component analysis (Noble, Wolmetz, Ochs, Farah, & McCandliss, 2006); and HOME, an index for home environment including home literacy environment (Segers et al., 2016). A battery of behavioral tests measuring intelligence, language and reading related skills was administrated. Verbal Comprehension, Concept Formation, and Visual Matching sub-tests of the Woodcock-Johnson III Tests of Cognitive Abilities (McGrew & Schrank, 2007), which have reliabilities of 0.80 or higher and have been used as a proxy for IQ, were used to estimate general cognitive abilities (Shaw, 2010). Vocabulary was measured with Peabody Picture Vocabulary Test (4th edition) (Dunn & Dunn, 2007). Blending, Elision, Memory for Digit, Nonword Repetition sub-tests from the Comprehensive Test of Phonological Processing (1st Edition) (CTOPP; Wagner, Torgesen, & Rashotte, 1999) were used to measure phonological skills. Finally, RAN (Objects and Colors sub-tests) (Wolf & Denkla, 2005) and Letter Identification sub-test of Woodcock Reading Mastery Test R/NU (WRMT-R/NU; Mather, 1998) were administered.
The same set of tests was used at $t_2$. Numbers and Letters sub-tests of RAN were further included at $t_2$ to measure print-sound mapping efficiency. Additionally, tests measuring different aspects of reading ability were administrated at $t_2$, including Sight Word Efficiency and Phonemic Decoding Efficiency sub-tests from the Test of Word Reading Efficiency (1st Edition) (TOWRE; Torgesen, Wagner, & Rashotte, 1999), Word Identification, Word Attack, and Passage Comprehension sub-tests from WRMT-R/NU, and Reading Fluency and Spelling sub-tests from WJ-III Tests of Achievement. Details of these measures can also be found in our previous papers (Black et al., 2012; Myers et al., 2014).

**Image acquisition**

High-resolution T1-weighted images (fast spoiled gradient echo) for each child were collected at both time-points with the following parameters: 128 slices; thickness = 1.2 mm; NEX = 1; repetition time (TR) = 8.5 ms; echo time (TE) = 3.4 ms; inversion time (TI) = 400 ms; in-plane resolution = 256 × 256; voxel size = 0.9 × 0.9 × 1.2 mm; flip angle (FA) = 15 °; field of view (FOV) = 22 cm. High-angular resolution diffusion-imaging (HARDI; single-shot spin-echo, echo-planar imaging sequence) were collected at $t_2$ with the following parameters: 46 axial slices; slice thickness = 3 mm; repetition time (TR) = 5000 ms; echo time (TE) = 81.7 ms; in-plane resolution = 128 × 128; voxel size = 2.0 × 2.0 × 3.0 mm³; 150 directions with $b = 2500$ s/mm²; 6 volumes with $b = 0$ s/mm². All images were acquired using a GE Healthcare 3.0 T 750 scanner with eight-channel phased-array head coil at Richard M. Lucas Center for Imaging at Stanford University.
Behavioral data analyses

To reduce dimensionality of behavioral metrics, two factor analyses were conducted on reading-related tests for t1 and t2 separately; t1: Blending, Elision, Memory for Digits, Nonword Repetition sub-tests of CTOPP, Objects and Colors sub-tests of RAN, Letter Identification sub-test of WRMT; and t2: Blending, Elision, Memory for Digits, Nonword Repetition sub-tests of CTOPP, Numbers, Letters, Objects and Colors sub-tests of RAN, Sight Word Efficiency and Phonemic Decoding Efficiency sub-tests of TOWRE, Word Identification, Word Attack, Passage Comprehension sub-tests of WRMT-R/NU, Reading Fluency and Spelling sub-tests of WJ-III Tests of Achievement. In each analysis, Maximum Likelihood was used as the extraction method, Varimax was used as the rotation approach, and Bartlett method was used to calculate factor scores. From t1 behavioral metrics, we obtained two factors using the criteria of eigenvalues greater than 1 (Table S3). These factors together explained 53.8% of the total variance. Since PA and RAN loaded heavily on each factor, respectively, we named them as t1PA and t1RAN (letter knowledge contributes to both factors, but more to t1PA). Since PA, RAN, and letter knowledge have been repeatedly shown to be the most robust and reliable measures for predicting reading development in alphabetic languages (Caravolas et al., 2012; Hulme et al., 2005; Hulme & Snowling, 2013), we used these two scores as precursors of reading in subsequent analyses. Using the same approach, we obtained three factors from t2 metrics, which explained 67.2% of the total variance.
and were named as $t_2$READ, $t_2$PA, and $t_2$RAN according to the factor loading scores (Table S4).

To test our hypothesis about the relationship between APA and reading, we first performed simple correlation. Once significant correlation between PatAGE and $t_2$READ was observed, three hierarchical multiple regressions were further conducted to test three hypotheses in the following order: (1) APA effect remains significant after controlling for demographic variables; (2) APA effect is present above and beyond other familial factors; (3) APA effect is not explained by $t_1$ cognitive-linguistic skills ($t_1$PA and $t_1$RAN) generally known to be highly heritable and is relatively independent of these precursors. Therefore, in the first model, we entered demographic variables ($t_2$ age, gender, handedness and average pIQ from $t_1$ and $t_2$) in the first step and PatAGE in the second step (Model 1 in Table 1). In the second model, besides the aforementioned nuisance variables, we additionally regressed out birth order (Price, 2008), parental reading history (van Bergen et al., 2015), SES (Pan et al., 2016), home literacy environment (Segers et al., 2016), which are known to be associated with reading; and maternal age, which was highly correlated with PatAGE (Edwards & Roff, 2010; Saha et al., 2009) (Model 2 in Table 1). In the third (final) model, $t_1$PA and $t_1$RAN (Hulme et al., 2005) were additionally entered in the third step, just before PatAGE was entered (Model 3 in Table 1), to examine whether the APA effect was present beyond $t_1$ cognitive-linguistic skills. All statistics were done with SPSS 21.0 (IBM, Inc.), and $p$-values were two-tailed while statistical significance was set at 0.05.
One main aim of this study was to explore the cognitive mechanisms underlying the APA effect, e.g., whether the APA effect on reading was mediated by cognitive-linguistic precursors such as PA. But since \( t_1 \)RAN and \( t_1 \)PA showed no significant correlations with PatAGE, no further mediation models were established with \( t_1 \)RAN or \( t_1 \)PA as mediators.

**Structural image preprocessing**

Both cross-sectional and longitudinal analyses were conducted with VBM8 (http://www.neuro.uni-jena.de/vbm/), a toolbox for SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/), implemented in Matlab (Mathworks). For the across-sectional analyses at \( t_1 \) and \( t_2 \), individual T1 volumes were first segmented into gray matter, white matter and cerebrospinal fluid with a resampling at 1.5 mm\(^3\). Then, the gray matter segments were registered to a T1 template in MNI-space (Montreal Neurological Institute) by using both affine normalization and Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) (Ashburner, 2007), and subsequently modulated by the ‘affine and non-linear’ modulation (http://www.neuro.uni-jena.de/vbm/segmentation/modulation/). The modulated images containing regional tissue volume of gray matter for each voxel were smoothed with an 8-mm full-with half-maximum isotropic Gaussian kernel. Voxels with gray matter values < 0.1 were excluded (i.e., absolute threshold masking) to avoid possible edge effects.
As for the longitudinal VBM analysis, ‘Preprocessing of Longitudinal Data’ module in VBM8, which contains specific preprocessing steps was used. Intra-subject realignment, bias correction, segmentation, and normalization (Ashburner, 2007) were done sequentially as described elsewhere (Ridgway et al., 2007). After applying spatial smoothing with an 8-mm full-width half-maximum Gaussian kernel, we obtained maps of gray matter volume for both time-points. We generated GMV maps reflecting change from t1 to t2 for further analyses (such that a positive change would indicate growth from t1 to t2).

**Whole-brain regression analyses**

First, we examined the correlations between PatAGE and global measurements, i.e., t1TIV (defined as the sum of total gray matter, white matter and cerebrospinal fluid) and t2TIV. Then, we examined whether PatAGE correlated with ∆TIV between two time-points (such that a positive change would indicate growth from t1 to t2) while controlling for the baseline (i.e., t1TIV). After that, to examine relationships between regional GMV at each time-point, as well as ∆GMV with PatAGE, voxel-wise whole brain regression was conducted while controlling for the effect of global measurements. Specifically, t1TIV or t2TIV was controlled in cross-sectional analyses for t1 and t2, respectively. In the longitudinal analysis, t1TIV and ∆TIV were controlled to exclude effects from initial gross volume and its development. Since no significant correlations between t1TIV, ∆TIV, and PatAGE (all p’s > 0.1), the model was free from multicollinearity. Topological FWE correction implemented in SPM8 was used to determine corrected thresholds of statistical
significance. All clusters significant at a threshold of corrected $p < 0.05$ corrected for
the whole brain ($p$-voxel < 0.005 for height) were reported in Montreal Neurological
Institute (MNI) space. Since no significant clusters were found for voxel-wise
analyses at either time-point $t_1$ or $t_2$, all further analyses focused on longitudinal
changes. In particular, for significant clusters, region-of-interest (ROI) analyses
were conducted to examine the robustness of the effect. For this purpose, value of
each voxel in the cluster was extracted and averaged, then put in the hierarchical
multiple regression analyses as the dependent variable. First, demographic
variables ($t_1$ age, time interval between $t_1$ and $t_2$, gender, handedness, average of $t_1$
and $t_2$ pIQ), $t_1$TIV and $\Delta$TIV were entered in the first step, while PatAGE was
entered in the second step. Secondly, we further controlled for MatAGE and
MatARHQ since they showed significant correlation with PatAGE.

Next, we examined the relationship between $\Delta$GMV and children’s $t_2$READ
in the cluster that was significantly associated with PatAGE (i.e., the APA-cluster,
which was in the left thalamus) by using small volume correction ($p$-voxel < 0.005,
$p$-cluster < 0.05, topological FWE correction) while $t_1$TIV and $\Delta$TIV were
statistically controlled. The mean $\Delta$GMV was calculated from this APA-cluster in
the left thalamus for subsequent ROI analyses. Then, hierarchical multiple
regression analyses were conducted to test for the robustness of the effect. In the
first model, $t_2$READ was the dependent variable and demographic variables ($t_2$ age,
gender, handedness, average pIQ), $t_1$TIV and $\Delta$TIV were entered in the first step. In
the second model, $t_1$ cognitive-linguistic skills (i.e., $t_1$PA and $t_1$RAN) were further
entered in the second step since they were also significant predictors of $t_2$READ in previous analysis. The average $\Delta$GMV was entered in the final step.

**Mediation analyses**

In the region where volumetric change significantly correlated with both PatAGE and $t_2$READ, we used mediation as the conceptually preferred model to examine whether the negative impact from APA on reading was mediated by brain maturation. To test indirect effects, bootstrapping (10,000 samples) was used to obtain 95% confidence intervals. We first ran a basic model without controlling for covariates. If a significant indirect effect existed (i.e., confidence intervals do not overlap zero), we further adjusted the model for demographic variables ($t_2$ age, gender, handedness, average pIQ), $t_1$TIV, $\Delta$TIV, and $t_1$ cognitive-linguistic precursors ($t_1$RAN and $t_1$PA) to confirm the uniqueness and robustness of the effect.

Recently, PA has been reported to partially mediate the effect of parental reading on offspring’s reading (van Bergen et al., 2015). If we replicate this result, we can (to some extent) make inferences about multi-level intergenerational transmission, together with the APA findings. Because we found significant correlations between MatARHQ and $t_1$PA, MatARHQ and $t_2$READ, $t_1$PA and $t_2$READ (Table S2), we thus tested whether there was a mediating role of $t_1$PA on the relationship between MatARHQ (as a proxy for parental reading) and $t_2$READ. Age at $t_2$, gender, handedness, average pIQ, and $t_1$RAN were further controlled.
PROCESS procedure (release 2.16.1) implemented in SPSS was used to conduct mediation analyses (Hayes, 2013).

Atlases, large datasets and diffusion imaging data used to examine the location and connectivity patterns of VBM findings

We examined fine-grained spatial localization and connectivity patterns of the APA-cluster capitalizing on the fact these have been shown to inform possible functional roles of a particular brain region (in this case, the left thalamic area) in the absence of a comprehensive set of cognitive and behavioral measures. We therefore adopted multiple complementary analytical approaches to obtain more information about fine-grained spatial localization and connectivity patterns. First, we spatially localized the APA-cluster using two brain atlases. (1) MOREL ATLAS: The thalamus consists of several nuclei where each are associated with different functions. We therefore calculated the number and percentage of voxels that overlapped with the APA-cluster and each thalamic nucleus from the Morel Atlas, a histological atlas that is optimal for thalamic targets, which is in MNI-space (for details, see Jakab et al., 2012; Krauth et al., 2010); (2) OXFORD THALAMIC CONNECTIVITY PROBABILITY ATLAS: The structural connectivity patterns provides information about function of a given region (Barron et al., 2015; Behrens et al., 2003). We therefore used Oxford Thalamic Connectivity Probability Atlas with the atlasquery tool implemented in FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases) to obtain the probability that the APA-cluster is structurally connected to different cortical areas (de Moura et al., 2016).
Next, to further understand the functional role of the APA-cluster and complementary to the results from analyses using the histological and diffusion imaging atlases, we examined APA-cluster-associated cortical patterns by using an online database, Neurosynth (v0.5; Yarkoni et al., 2011). In particular, we generated a co-activation map by including all fMRI studies in the database (N > 10,900) and used the whole APA-cluster as ROI. A threshold of False Discovery Rate (FDR) at $p < 0.01$ was used to obtain significant regions that is most likely to be reported in fMRI studies when the APA-cluster is also reported (i.e., forward inference). In addition, we generated a seed-based whole-brain RSFC map by using data of 1,000 individuals from the 1,000 Functional Connectome Dataset (Biswal et al., 2010; Yeo et al., 2011). The center of gravity (COG) of the APA-cluster (MNI: $x = -19, y = -28, z = 6$) was used as the seed, and functional connectivity from the seed to the rest of the brain was calculated. The resultant map was thresholded with a liberal cutoff value of $r = 0.01$ as in the previous literature (Yang, Rosenblau, Keifer, & Pelphrey, 2015). To be more conservative, we took the co-activation map that overlapped with the RSFC map. Dice coefficients between the conjunction map and the seven large-scale intrinsic connectivity networks (visual, somatomotor, dorsal attention, ventral attention, limbic, frontoparietal, and default networks) from Yeo et al. (2011) were then calculated to examine which functional network may most overlap with the APA-cluster-associated cortical pattern.

In the final step, these results were confirmed by analyzing white matter connectivity, where fibers passing the APA-cluster were reconstructed using
deterministic tractography. Diffusion-weighted imaging preprocessing was performed by using ExploreDTI (http://www.exploredti.com; A Leemans, Jeurissen, Sijbers, & Jones, 2009). The pre-processing steps consisted of visual quality assurance and rigorous motion and eddy current correction with the required reorientation of the b-matrix (Alexander Leemans & Jones, 2009). The diffusion tensors were calculated using a non-linear regression procedure (Pierpaoli & Basser, 1996). The individual datasets were non-rigidly normalized to MNI (Montreal Neurological Institute) space. Next, whole brain tractography was performed for each individual dataset using a deterministic approach (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000). Fibers (streamlines) were reconstructed by defining seed points distributed uniformly throughout the data at 2.0 × 2.0 × 2.0 resolution, following the main direction with step size set at 1.0 mm. Fiber tracking was discontinued when the fiber entered a voxel with FA < 0.2 or made a high angular turn (angle > 40°), or when the fiber was outside the fiber length range of 50-500 mm. Two analyses were then conducted: (1) To localize fibers and get a general view, the cluster related to PatAGE was used as ROI and all fibers passing through this cluster were delineated. The delineated fibers and its projection points were visually inspected, after which individual maps were binarized and summed to acquire probabilistic map across participants. (2) To complement the Neurosynth analysis above and to identify the functional network most relevant to the APA-cluster, the numbers of streamlines passing through the APA-cluster and each of the 7 functional networks from the Yeo et al. (2011) were calculated and normalized by
dividing this number by size of the target network. The results were treated as the connectivity strength and compared between networks with one-way ANOVA (as well as post-hoc analyses). Furthermore, we examined the correlations between the connectivity strength with PatAGE as well as with $t_2$READ.

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RUNNING HEAD: THALAMUS LINKS PATERNAL AGE AND OFFSPRING'S READING

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Author Contributions

F. Hoeft designed the study and collected data with her students. F. Hoeft, Z.C. Xia and C. Wang conceived the particular idea of the manuscript. Z.C. Xia, C. Wang and M. Vandermosten analyzed the data. Z.C. Xia, F. Hoeft, C. Wang, R. Hancock, and M. Vandermosten cowrote the manuscript.

Data Availability

Data that support the findings of this study are available from the corresponding author on request.

Conflict of interest

The authors declare no competing financial interests.
Figure Legends

Figure 1. Distribution of paternal age at childbirth (PatAGE) and its relationship with reading. A. A frequency plot displaying the distribution of PatAGE in the current study. B. A scatter plot showing the correlation between PatAGE and offspring’s reading composite scores. Reading scores were calculated by using factor analysis on a battery of reading-related tests (see ‘behavioral data analyses’ in main text for details), and adjusted for demographic variables (age, gender, handedness and performance intelligence quotient) at time-point 2 (grade 3). The linear regression line and $R^2$ are shown in the plot.

Figure 2. A. Brain regions that are associated with paternal age at childbirth (PatAGE) and composite score of reading at time-point 2 ($t_{2\text{READ}}$). Significant clusters were identified from: (1) whole brain voxel-wised regression analyses between gray matter volume change ($\Delta$GMV) and PatAGE regressing out total intracranial volume (TIV) at time-point 1 ($t_{1\text{; kindergarten}}$) and change of TIV ($\Delta$TIV) between time-point 1 and 2 ($t_{2\text{; grade 3}}$) (yellow), and (2) between $\Delta$GMV and $t_{2\text{READ}}$ within the PatAGE related cluster (cyan). Threshold: $p$-voxel < 0.005 (height), topological family wise error correction of $p$-cluster < 0.05. B. A scatter plot representing the relationship between yellow cluster in A and PatAGE. The mean average of values calculated by subtracting $t_{2}$ to $t_{1}$ GMV images from all voxels of the yellow cluster are plotted against PatAGE. $\Delta$GMV is residualized for $t_{1}$TIV and $\Delta$TIV. The linear regression line is displayed in the plot. C. A scatter plot
representing the relationship between cyan cluster in A and reading. The mean
average of values calculated by subtracting $t_2$ to $t_1$ GMV images from all voxels of
the yellow cluster are plotted against $t_2$READ are plotted. $\Delta$GMV is residualized for
$t_1$ TIV and $\Delta$TIV. The linear regression line is displayed in the plot.

Figure 3. Relationship between paternal age at childbirth (PatAGE) and offspring’s
reading at time-point 2 ($t_2$READ). $t_2$READ can be significantly predicted by
PatAGE, and such effect is mediated by gray matter volume change in offspring’s
left thalamus from time-point 1 ($t_1$; kindergarten) to time-point 2 ($t_2$; grade 3). Age
at $t_2$, gender, handedness, average of $t_1$ and $t_2$ performance IQ, total intracranial
volume (TIV) at $t_1$, TIV change from $t_1$ to $t_2$, phonological composite score at $t_1$,
rapid naming composite score at $t_1$ were controlled in the model. The bias corrected
confidence intervals (95%) for indirect effect didn’t contain zero (low = -0.552, high =
-0.043), indicating the mediation is significant. Supplementary Figure 1 includes
complementary mediation analysis showing how family history, which typically
represents heritable risk, predicts reading outcome via phonological processing.

Figure 4. Localization and structural connectivity pattern of the posterior thalamic
region based on Morel and Thalamic Connectivity atlases. A. A bar plot displaying
the percentage of total voxels in the paternal age-related cluster (yellow cluster in
Figure 2A) overlaps with different divisions of the Morel atlas (Jakab et al., 2012;
Krauth et al., 2010). B. A bar plot showing the probability of the cluster belonging
to different subdivisions of the Thalamic connectivity atlas. The probability is
calculated by using ‘autoaq’ function implemented in FSL.
RUNNING HEAD: THALAMUS LINKS PATERNAL AGE AND OFFSPRING'S READING

(https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases). Acronyms: CL, central lateral nucleus; CM, central median nucleus; LP, lateral posterior nucleus; VLPv, ventral lateral posterior nucleus, ventral; VPI, ventral posterior inferior nucleus; VPL, ventral posterior lateral nucleus; VPM, ventral posterior medial nucleus.

Figure 5. Functional co-activation and connectivity patterns of the posterior thalamic region based on Neurosynth. A. A brain map representing overlapping regions between co-activation and resting-state functional connectivity (RSFC) maps where these maps were generated in Neurosynth with the seed being the center-of-gravity of the paternal age-related cluster (yellow cluster in Figure 2A). B. A bar plot showing the degree of overlap between the overlap map in A and the 7 functional networks derived from Yeo (2011) represented by Dice coefficients. Dice coefficient measures the similarity between the overlapping areas and a given function network, ranging from 0 to 1. While 0 indicates the two networks are disjoint, 1 indicates the two networks are identical. Acronyms: LH, left hemisphere; RH, right hemisphere.

Figure 6. Structural connectivity patterns (white matter tractography) of the posterior thalamic region using subject-specific diffusion imaging data. A. An example of reconstructed fibers in a representative child with the seed being the paternal age (PatAGE)-related cluster (APA-cluster; yellow cluster in Figure 2A). B. Intersection across children with diffusion imaging data (N = 23) is shown for demonstrative purposes. In particular, only fibers (i.e., streamlines) observed in more than 25% of the subjects (i.e., 6 children) are displayed. The color bar
represents the number of subjects where the streamline is observed in a given voxel.

C. The dorsal attention network (DAN) compared to the ventral attention network (VAN) derived from Yeo et al (2011) showed significantly greater number of streamlines (an index of structural connectivity) to go through the APA-cluster.

DAN- and VAN-related connectivity in each subject was defined as the number of streamlines that pass through the APA-cluster and the given network. Then the number was normalized by dividing the total number of streamlines by the size (volume) of the target network. D. A scatter plot shows a positive correlation between PatAGE and number of streamlines labeled as DAN passing through the APA cluster. The linear regression line and \( R^2 \) are shown. E. A scatter plot shows a negative correlation between reading composite scores at time-point 2 (grade 3) and the number of streamlines passing through the APA-cluster and DAN. The linear regression line and \( R^2 \) are shown. 

Acronyms: LH, left hemisphere; RH, right hemisphere.

**Figure 7.** A schematic diagram summarizing our current findings. Descriptions in brackets are potential mechanisms based on the past literature (see main text). Descriptions in gray font in a dotted square indicate findings from the past literature – studies have shown a greater role for genetic influences on parent-offspring correlations in the dorsal phonological pathway and processing, and more environmental influence on the ventral orthographic pathway and processing (Olson et al. 1989, Samuelsson et al. 2007).
### Tables

Table 1 Multiple linear regression analyses examining the unique contribution of paternal age on offspring’s reading performance at time-point 2

| Model | Step | Predictor     | $\Delta R^2$ | $\beta$   |
|-------|------|---------------|--------------|-----------|
| 1     | 1    | Age ($t2$)    | 0.284 *      | -0.351 *  |
|       |      | Gender        | -0.022       |           |
|       |      | Handedness    | 0.081        |           |
|       |      | Average pIQ   | 0.302 *      |           |
|       | 2    | PatAGE        | 0.146 **     | -0.393 ** |
| 2     | 1    | Age ($t2$)    | 0.279 *      | -0.296    |
|       |      | Gender        | 0.026        |           |
|       |      | Handedness    | 0.093        |           |
|       |      | Average pIQ   | 0.200        |           |
|       | 2    | Birth Order   | 0.237 †      | -0.178    |
|       |      | MatAGE        | 0.245        |           |
|       |      | PatARHQ       | -0.100       |           |
|       |      | MatARHQ       | -0.200       |           |
|       |      | SES           | -0.189       |           |
|       |      | HOME          | 0.224        |           |
| 3     | 1    | PatAGE        | 0.095 *      | -0.522 *  |
|       |      | Age ($t2$)    | 0.279 *      | -0.247    |
|       |      | Gender        | -0.012       |           |
|       |      | Handedness    | 0.106        |           |
|       |      | Average pIQ   | -0.020       |           |
|       | 2    | Birth Order   | 0.237 †      | -0.033    |
|       |      | MatAGE        | 0.113        |           |
|       |      | PatARHQ       | -0.088       |           |
|       |      | MatARHQ       | -0.122       |           |
RUNNING HEAD: THALAMUS LINKS PATERNAL AGE AND OFFSPRING’S READING

|   | SES    | HOME   |
|---|--------|--------|
| 3 | t1PA   | 0.138 * | 0.403 ** |
|   | t1RAN  | 0.307 * |
| 4 | PatAGE | 0.073*  | -0.469 * |

Note:

β’s are values at the final step (all predictors included).

Abbreviations: ARHQ, Adult Reading History Questionnaire; HOME, Home Observation Measurement of the Environment; Mat, maternal; PA, phonological awareness; Pat, paternal; pIQ, performance intelligence quotient; RAN, rapid naming; SES, socioeconomic status; t1, time-point 1; t2, time-point 2.

** p < 0.01; * p < 0.05, † p < 0.1
Figures

Figure 1
Figure 2

A BC

Paternal age Reading

Gray matter volume change from time-point 1 to 2

Paternal age (years)

Reading composite score at time-point 2

Gray matter volume change from time-point 1 to 2
Figure 3

Paternal age at childbirth

GMV change in the thalamus (offspring)

Path a: $\beta = 0.546, p = 0.002$

Path b: $\beta = -0.365, p = 0.025$

Path c: $\beta = -0.377, p = 0.009$

Path c': $\beta = -0.178, p = 0.245$

Reading (offspring)
Figure 4

A  Morel Atlas

B  Thalamic Connectivity Probability Atlas

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Figure 5

**A** Intersection of Neurosynth-Derived Maps

- Frontal eye field
- Inferior parietal sulci
- Middle temporal visual area

*Overlapping areas between co-activation and RSFC maps*

**B** Similarity with the Intrinsic Functional Networks

- Dorsal attention
- Ventral attention
- Visual
- Somatomotor
- Frontoparietal
- Default
- Limbic

*Dice Coefficient Similarity with the Intrinsic Functional Networks*
Figure 6

A. Diagram showing brain regions such as Prefrontal Cortex, Somatomotor Cortex, Posterior Parietal Cortex, Visual Area, Cerebellum, and Spinal Cord.

B. Brain images with labels: LH (left hemisphere) x = -34, z = -12, y = -7 and RH (right hemisphere) x = -25, z = 14, y = -7.

C. Graph showing t = 6.607, p < 0.001 for the comparison of dorsal attention versus ventral attention.

D. Scatter plot showing $R^2 = 0.24$ correlation between number of streamlines normalized by size of target networks and paternal age (years).

E. Scatter plot showing $R^2 = 0.20$ correlation between reading composite score at time-point 2 and number of streamlines normalized by the size of network.
Figure 7

Multifactorial Liability Potentially Contributing to Poor Reading

- **Paternal Age** (Genetic but not inherited risk, de novo mutation)
- **Family History** (Inherited risk)
- **Home Literacy** (Environmental risk)
- **Thalamic Development** (Attention)
- **Phonological Processing**
- **Orthographic Processing**

Reading

Population incidence

Liability for poor reading