Potential Brain Age Reversal after Pregnancy: Younger Brains at 4–6 Weeks Postpartum

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Abstract—Pregnancy is accompanied by complex biological adaptations, including extreme hormonal fluctuations. Moreover, changes on the endocrine level are accompanied by changes in cerebral anatomy, such as reductions in brain or gray matter volume. Since declining brain and tissue volumes are characteristic for normal aging, the question arises of whether such pregnancy-induced anatomical effects are permanent or transient. To answer this question, we acquired high-resolution brain image data of 14 healthy women in their mid-twenties to late thirties at two time points: within 1–2 days of childbirth (early postpartum) and at 4–6 weeks after childbirth (late postpartum). At both time points, we estimated the brain ages for each woman using a well-validated machine-learning approach based on pattern recognition. Ultimately, this algorithm – designed to identify anatomical correlates of age across the entire brain – reveals a single score for each individual: the BrainAGE index. Comparing the BrainAGE indices between both time points, female brains at late postpartum were estimated to be considerably younger than at early postpartum. On average, that difference was about five years (mean ± SD: 5.4 ± 2.4 years). These findings suggest a substantial restoration/rejuvenation effect after giving birth, which is evident already within the first couple of months.

INTRODUCTION

During pregnancy and the postpartum period, the maternal body undergoes tremendous adaptations, including extreme changes in hormone levels (Brunton and Russell, 2008). Perhaps surprising, being pregnant also seems to affect the gross anatomy of the brain, albeit existing research is extremely sparse – most likely due to the restrictions imposed on magnetic resonance imaging (MRI) during pregnancy. Nevertheless, at least two independent studies concluded that pregnancy is accompanied by significant decreases in brain and gray matter volumes (Oatridge et al., 2002; Hoekzema et al., 2017). As dwindling brain sizes and declining brain tissue in otherwise healthy subjects are common trademarks of brain aging (Raz et al., 2010; Pfefferbaum et al., 2013), the question arises as to whether any pregnancy-induced brain loss is permanent or transient. While the two aforementioned studies (Oatridge et al., 2002; Hoekzema et al., 2017) closely agree on various aspects, there seems to be some discrepancy on the endurance of the effect. More specifically, Oatridge and colleagues reported that brain size decreased during pregnancy, but then increased again after giving birth, with a relative restoration within the first few months postpartum (2002). Hoekzema and colleagues also reported gray matter reductions during pregnancy, but observed that most of the incurred loss actually persisted until at least two years after pregnancy (2017). A third study (Kim et al., 2010) compared gray matter between two time points after giving birth, more specifically between 2 and 4 weeks postpartum and 3–4 months postpartum, and revealed gray matter increases at the later time point. These latter findings (Kim et al., 2010) appear in line with the outcomes of the first study which examined brain and ventricle size (Oatridge et al., 2002), although the morphological substrate measured by Kim and colleagues (voxel-wise gray matter) is more similar to the second study (Hoekzema et al., 2017).

To shed further light on the nature of the effect (transient vs. persistent) – without tying our observations to a specific morphometric measure...
Our study sample included 14 right-handed, healthy postpartum women between 25 and 38 years of age. For sample characteristics, please refer to Table 1. All women had normal pregnancies, uncomplicated deliveries (vaginal: n = 9; Cesarean: n = 5) and at least one night of sleep following delivery. Moreover, all women were breastfeeding at the time of the follow-up (late postpartum) brain scan. Exclusion criteria were post pregnancy complications, admission of infants to the neonatal intensive care unit, ongoing depression or anxiety disorders, treatment with hormonal compounds and/or psychotropic drugs within three months prior to the study, as well as contraindications to MRI. All procedures were approved by the Regional Ethical Review Board, Uppsala (Sweden), and all participants provided written informed consent.

Table 1. Sample characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age: mean ± SD years (range)</td>
<td>32.8 ± 4.0 (25–38)</td>
</tr>
<tr>
<td>Pre-pregnancy BMI: mean ± SD kg/m² (range)</td>
<td>23.9 ± 2.8 (20.2–31.2)</td>
</tr>
<tr>
<td>Nordic origin: n (%)</td>
<td>13 (92.9)</td>
</tr>
<tr>
<td>Married or cohabiting: n (%)</td>
<td>13 (92.9)</td>
</tr>
<tr>
<td>University education: n (%)</td>
<td>11 (78.6)</td>
</tr>
<tr>
<td>Smokers: n (%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Non-pregnancy light-to-moderate alcohol use: n (%)</td>
<td>10 (71.4)</td>
</tr>
<tr>
<td>First delivery: n (%)</td>
<td>7 (50.0)</td>
</tr>
<tr>
<td>Singleton pregnancy: n (%)</td>
<td>14 (100)</td>
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BMI = body mass index, SD = standard deviation.

Brain image acquisition and processing

High-resolution T1-weighted brain images were acquired at 27 ± 10 h (early postpartum) and at 34 ± 5 days (late postpartum) after delivery. For this purpose, we used a whole-body scanner (Achieva 3T X; Philips Medical Systems, Best, The Netherlands) equipped with an eight-channel head coil applying the following parameters: 5700-ms repetition time, 15-ms echo time, 400-ms inversion time, 90° flip angle, and 0.45 × 0.45 × 2.0 mm³ voxel size. As described elsewhere (Luders et al., 2016), the acquired brain images were processed in Matlab (http://www.mathworks.com/products/matlab/), using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html), resulting in spatially normalized and smoothed gray matter segments. Using these gray matter segments, the individual brain ages were estimated, as further described in the next paragraph, ultimately revealing a so-called BrainAGE index.

The BrainAGE index

The BrainAGE framework utilizes relevance vector regression, a machine-learning approach based on pattern recognition (Franke et al., 2010, 2012a,b). It has been initially trained using brain scans and aging information of more than 650 subjects, ranging between 19 and 86 years of age. Importantly, those subjects are not part of the current sample. When applied to new brain scans – specifically the processed gray matter segments – of the current sample, the trained algorithm generates an estimated brain age. The difference between estimated age and true chronological age yields the so-called brain [Age] [Gap] [E]stimate (BrainAGE). For example, if the algorithm computes +5 for the brain of a 32-year-old, this individual shows the typical aging pattern of a 37-year old. Conversely, if the algorithm computes -5 for the brain of a 32-year old, this individual shows the typical aging pattern of a 27-year old. In the current study, a BrainAGE index was calculated at early postpartum as well as at late postpartum for each of the 14 women.

Hormonal analysis

Blood samples for the hormonal analyses were drawn approximately twenty minutes prior to each brain-
The mean difference between the two time points was ranged between 1.7 and 8.3 years (median: 5.64 years). In Fig. 1, the magnitude of the change in BrainAGE compared to the early phase of postpartum. As shown indicating considerably younger brains during the late contrast, the BrainAGE at late postpartum (i.e., at 4–6 weeks after delivery) was 1.35 ± 3.61 years. In Table 2, serum concentrations of estradiol as well as of progesterone were significantly lower at late postpartum compared to early postpartum (estradiol: T = −10.51, p < 0.001, d = −7.01; progesterone: T = −8.97, p < 0.001, d = −5.98). While there was no significant correlation between serum concentrations and BrainAGE at either time point, the link was significant across both time points for both hormones (estradiol: T = 5.77, p < 0.001, r = 0.78; progesterone: T = 5.01, p < 0.001, r = 0.74), with lower values for all measures at late compared to early postpartum. There were no significant correlations between changes in BrainAGE and changes in serum concentrations. Individual measures for BrainAGE, log10-estradiol, and log10-progesterone are depicted in Table 2.

**RESULTS**

**BrainAGE**

The BrainAGE (mean ± SD) at early postpartum (i.e., within 1–2 days of delivery) was 1.35 ± 3.61 years. In contrast, the BrainAGE at late postpartum (i.e., at 4–6 weeks after delivery) was −4.02 ± 3.09 years, indicating considerably younger brains during the late compared to the early phase of postpartum. As shown in Fig. 1, the magnitude of the change in BrainAGE ranged between 1.7 and 8.3 years (median: 5.64 years). The mean difference between the two time points was more than five years (5.36 ± 2.4 years) constituting a robust effect (T = −8.37, p < 0.001, d = −4.64).

**Hormone levels and links to BrainAGE**

As shown in Table 2, serum concentrations of estradiol as well as of progesterone were significantly lower at late postpartum compared to early postpartum (estradiol: T = −10.51, p < 0.001, d = −7.01; progesterone: T = −8.97, p < 0.001, d = −5.98). While there was no significant correlation between serum concentrations and BrainAGE at either time point, the link was significant across both time points for both hormones (estradiol: T = 5.77, p < 0.001, r = 0.78; progesterone: T = 5.01, p < 0.001, r = 0.74), with lower values for all measures at late compared to early postpartum. There were no significant correlations between changes in BrainAGE and changes in serum concentrations. Individual measures for BrainAGE, log10-estradiol, and log10-progesterone are depicted in Fig. 2.

**Table 2. Levels of estradiol and progesterone**

<table>
<thead>
<tr>
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<th>Estradiol (pmol/l)</th>
<th>Progesterone (nmol/l)</th>
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<tr>
<td>Early postpartum</td>
<td>1533 ± 694</td>
<td>41.9 ± 37.4</td>
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<tr>
<td>Late postpartum</td>
<td>118 ± 55</td>
<td>0.8 ± 0.5</td>
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*Serum levels were missing for 4 individuals at early postpartum.

pmol/l = picomoles per liter.

nmol/l = nanomoles per liter.
A significant change in estrogen/progesterone levels (i.e., from a manifold increase during pregnancy to almost non-measurable levels after birth) is one of the characteristics of the maternal body. However, the full effect of the postpartum endocrine changes manifests only a few days after giving birth. This is not only evident in the actual hormonal measures but also reveals itself, for example, as an adjustment period during which performance on hormone-sensitive tasks is successively normalized (Kask et al., 2008). Thus, even though serum hormone concentrations have already started to decline, there is a small window of opportunity to study the maternal brain during the very early postpartum period as an approximation of the pregnant brain.

Contrasting such very early postpartum measures (i.e., obtained within 1–2 days of giving birth) with later postpartum measures (i.e., obtained at 4–6 weeks after giving birth), our findings extend existing work in this understudied field of research (Oatridge et al., 2002; Kim et al., 2010; Hoekzema et al., 2017). The current analyses revealed significantly lower brain ages (i.e., seemingly younger brains) at the follow-up time point compared to the initial time point.

Correspondence with previous research outcomes

Altogether, these findings seem to suggest a substantial restoration/rejuvenation effect after giving birth, which is evident already within 4–6 weeks postpartum. Prior research suggested that brain and tissue volumes – albeit initially decreasing during pregnancy – are restored within the first few months after giving birth (Oatridge et al., 2002; Kim et al., 2010). Our findings are consistent with those reports in that restored brain and tissue volumes may be reflections of seemingly younger brains. In other words, the calculated time- and subject-specific BrainAGE index is based on the tissue concentrations in specific brain regions (i.e., those deemed as age-relevant when training the algorithm). Since aging is accompanied by dwindling brain tissue, increased volumes at late postpartum as compared to early postpartum (as observed by the two aforementioned studies) translate to lower brain ages at late postpartum versus early postpartum (as observed in the current study). In contrast, another study suggested that pregnancy-induced gray matter reductions endured for at least a few years (Hoekzema et al., 2017). However, even in that latter study it was observed that there was a partial volume recovery in the hippocampus, a brain region known to be extremely plastic and amenable to structural changes due to synaptogenesis, angiogenesis, dendritogenesis – and perhaps even neurogenesis (Eriksson et al., 1998), although the latter is not unequivocally supported (Sorrells et al., 2018). Moreover, the hippocampus is also one of the key structures implicated in brain aging (Fraser et al., 2015; Kurth et al., 2017). Thus, the hippocampus-specific tissue regain, as reported by Hoekzema and colleagues (2017) even if only evident after two years, appears somewhat in line with the direction of the current outcomes measuring BrainAGE, a com-

Fig. 2. Individual measures at early postpartum and at late postpartum. BrainAGE is indicated in years, estradiol in pmoI/l, and progesterone in nmol/l. For the latter two measures log10-scaled values were used. The 14 different colors refer to the 14 individuals. At early postpartum, serum measures were missing for four individuals.

The very narrow time frames within which all subjects were scanned at early/late postpartum, the combination of relevant hormonal data with high-resolution neuroimaging data, as well as a well-validated state-of-the-art approach estimating, automatically and objectively, the age of individual brains. Limitations of the current study are the small sample size as well as the lack of any pre-pregnancy hormonal and/or imaging data. In addition to addressing these limitations, it would be desirable in future studies to obtain additional post-pregnancy data (e.g., a third brain scan) after more than only 4–6 weeks as well as data from a control group, possibly of women who spent an equal amount of time in clinical care. Follow-up research might consider collecting alternative endocline and other measures known to change during pregnancy and the postpartum period, such as related to cortisol, oxytocin, or monoamine oxidase activity, just to name a few (Nissen et al., 1995; Meinschmidt et al., 2010; Sacher et al., 2016). In addition to biological factors, the cognitive and behavioral demands of motherhood (or parenthood in general) are likely to shape and remodel the brain of the caregiver (Anderson and Rutherford, 2012; Abraham et al., 2014). Thus, future studies might further advance this field of research by obtaining relevant non-biological information (e.g., measures of affective processing, attachment, mother-infant interactions). Last but not least, as reviewed and discussed elsewhere (Cole and Franke, 2017), the field of brain age prediction is rapidly evolving. Thus, rather than relying on T1-weighted data alone, future studies might benefit from using a combination of multiple neuroimaging modalities (e.g., T1-weighted, T2-weighted, and diffusion-weighted data) to further enhance the prediction performance of the machine-learning approach.

ACKNOWLEDGMENTS

This study was supported by a research grant from the Swedish Research Council to I.S.P. (K2014-54X-20642-07-4). In addition, E.L. is funded by the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the National Institutes of Health (R01HD081720).

REFERENCES


(Received 3 April 2018, Accepted 3 July 2018)