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Becoming a mother entails anatomical changes in the ventral striatum of the human brain that facilitate its responsiveness to offspring cues

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ABSTRACT

In mothers, offspring cues are associated with a powerful reinforcing value that motivates maternal care. Animal studies show that this is mediated by dopamine release into the nucleus accumbens, a core component of the brain's reward system located in the ventral striatum (VStr). The VStr is also known to respond to infant signals in human mothers. However, it is unknown whether pregnancy modifies the anatomy or functionality of this structure, and whether such modifications underlie its strong reactivity to offspring cues. Therefore, we analyzed structural and functional neuroimaging data from a unique pre-conception prospective cohort study involving first-time mothers investigated before and after their pregnancy as well as nulliparous control women scanned at similar time intervals. First, we delineated the anatomy of the VStr in each subject's neuroanatomical space and examined whether there are volumetric changes in this structure across sessions. Then, we tested if these changes could predict the mothers' brain responses to visual stimuli of their infants. We found decreases in the right VStr and a trend for left VStr reductions in the women who were pregnant between sessions compared to the women who were not. Furthermore, VStr volume reductions across pregnancy were associated with infant-related VStr responses in the postpartum period, with stronger volume decreases predicting stronger functional activation to offspring cues. These findings provide the first indications that the transition to motherhood renders anatomical adaptations in the VStr that promote the strong responsiveness of a mother's reward circuit to cues of her infant.

1. Introduction

Pregnancy involves radical hormone surges that trigger adaptations in the female body and brain, which benefit the protection and development of the fetus (Brunton and Russell, 2008). Furthermore, these adaptations also facilitate the postpartum care and protection of mammalian offspring, whose survival depends on the rapid onset and adequate expression of maternal caregiving. Hormonal priming of the mother's brain stimulates the emergence of maternal behaviors, a set of species-specific behaviors that promote the survival and optimal development of the highly dependent offspring (Brunton and Russell, 2008; Kohl and Dulac, 2018; Leuner et al., 2010; Lonstein et al., 2015; Numan, 2006; Numan and Woodside, 2010). Hormonal fluctuations in human gestation and parturition, acting in concert with other prenatal

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factors (Farre-Sender et al., 2018; Jones et al., 2019; Marques et al., 2013; Simon et al., 2009), have also been associated with diverse aspects of postpartum child health and development and the emergence of maternal attachment (Bergman et al., 2010; Levine et al., 2007; O'Connor et al., 2013; Olza-Fernandez et al., 2014).

Animal studies show that changes in the hedonic value allocated to pups play a central role in triggering the maternal drive to approach and care for the young. While virgin female rats generally display avoidant or aversive reactions to pup odors, for maternal animals these represent a strongly rewarding stimulus and potent reinforcer (Fleming et al., 1989, 1994). For instance, studies in various mammalian species have shown that pregnant and postpartum females bar-press for contact with newborns (Hauser and Gandelman, 1985; Lee et al., 2000; Pryce et al. 1993; Wilsoncroft, 1969). Accordingly, using a place preference paradigm, maternal rats have been demonstrated to prefer pup-associated chambers to chambers coupled with other rewards, such as cocaine or food (Fleming et al., 1994; Mattson et al., 2001).

The powerful reinforcing value associated with stimuli of the young is mediated by the activation of the mesolimbic reward circuit. This circuit is thought to act as a driving force in translating biologically relevant stimuli into adaptive responses and plays a key role in the emergence of maternal behavior due to its role in motivation, reward and the hedonic value of stimuli (Brunton and Russell, 2008; Kohl and Dulac, 2018; Leuner et al., 2010; Lonstein et al., 2015; Numan, 2006; Numan and Woodside, 2010). In maternal animals, this system is recruited by exposure to pup-related stimuli. For instance, a functional magnetic resonance imaging study in postpartum rats demonstrated that pup suckling strongly activates brain regions pertaining to the reward system (Febo et al., 2005; Ferris et al., 2005). In fact, suckling-induced activation exceeded the neural response to cocaine within these reward-related areas (Ferris et al., 2005).

In response to pup cues, projections from the medial preoptic area to the ventral tegmental area trigger dopamine release into the nucleus accumbens, a core node of the mesolimbic reward circuit that integrates multiple mesolimbic dopaminergic afferents and glutamatergic corticolimbic projections (Haber and Knutson, 2010; Ikemoto, 2007; Knutson and Cooper, 2005; Robbins and Everitt, 1996). This pup-induced recruitment of the mesolimbic reward circuit is critical for the expression of adequate maternal behaviors. For instance, lesions to the nucleus accumbens shell disrupt pup retrieval (Li and Fleming, 2003), and low levels of maternal care are associated with reduced dopamine release in response to pup cues within the nucleus accumbens (Champagne et al., 2004). Pup-associated cues, mediated by dopamine signaling in the nucleus accumbens, thus represent a powerful reinforcer for maternal animals that motivate the approach and caregiving of pups.

Hormonal priming of the brain during late pregnancy and parturition plays a central role in the switch from pup avoidance to approach and the induction of maternal behaviors (Brunton and Russell, 2008; Kohl and Dulac, 2018; Leuner et al., 2010; Lonstein et al., 2015; Numan, 2006; Numan and Woodside, 2010). Studies in various animal species have shown that pregnancy hormones can trigger maternal motivation. For instance, pregnancy-mimicking hormone treatments in female rodents and monkeys have been demonstrated to increase the frequency of bar pressing for stimuli related to the young and induce a preference for young animals over food (Champagne et al., 2004; Li and Fleming, 2003, Pryce et al., 1993). Pregnancy thus involves shifts in pup-associated hedonic value and represents a sensitive period for priming the reward circuit to optimally respond to offspring cues.

In humans, fMRI studies have also shown that the ventral striatum (VStr) —the region containing the nucleus accumbens—is activated in mothers in response to pictures or sounds of their child (Atzil et al., 2011; Lorberbaum et al., 2002; Strathearn et al., 2008; Swain, 2011), and the mesolimbic reward circuit is considered a crucial part of the human maternal brain (Barba-Müller et al., 2019; Kim et al., 2015). Links between the response of the VStr to infant cues and maternal behavior have also been observed in human mothers. For instance, mothers displaying primarily synchronous caregiving behaviors more strongly activate the VStr in response to movies of their infants than mothers showing mainly intrusive behaviors, and VStr activity is functionally correlated with emotion regulation, theory of mind and empathy networks, known to play a key role in human maternal behavior (Atzil et al., 2011). In a previous study, we have shown that pregnancy renders pronounced changes in the grey matter volume of the human brain, located primarily in higher-order association areas of the cortex involved in social cognition (Hoekzema et al., 2017). However, it is unknown whether pregnancy is associated with changes in the mesolimbic reward circuit that prepare a woman's brain to maximally respond to offspring cues. We hypothesized that pregnancy entails modifications in the VStr that are associated with its subsequent functional response to the women's infants.

We have previously shown that the cortical morphometric changes taking place during pregnancy highly resemble those that occur during adolescence (Carmona et al., 2019), and we expect that the relation between anatomy and function with regard to pregnancy-related neuroplasticity follows a pattern similar to that observed in adolescence. Studies in adolescent samples have found a negative correlation between grey matter cortical thickness and the magnitude of activation, with a thinner cortex in fronto-parietal regions being associated with a stronger activation of these areas while performing tasks recruiting those regions (Lu et al., 2009; Nunez et al., 2011). The biological mechanisms mediating this inverse relation are unknown, but synaptic pruning is considered to play an important role. Synaptic pruning during developmental periods could not only contribute to decreasing the thickness of the cortex but also increase the efficiency and selectivity of synaptic activity, thus producing greater activation (Anurova et al., 2015). Therefore, we predicted that stronger volume reductions in the VStr would be associated with a stronger activation of this region in response to offspring cues.

In this study, we measured VStr volume in structural magnetic resonance imaging (MRI) brain scans of first-time mothers investigated before and after their pregnancy, using a unique prospective pre-conception cohort neuroimaging dataset (Hoekzema et al., 2017). Considering the lack of clear signal intensity boundaries that hampers the automatic demarcation of the VStr (Patenaude et al., 2011; Loh et al., 2014; Nugent et al., 2013), we used a reliable previously established manual delineation approach for investigating VStr anatomy (Carmona et al., 2009, 2012; Gunduz et al., 2002; Hoekzema et al., 2014). We then compared the VStr volumetric changes observed in first-time mothers to those obtained in a control group of nulliparous women scanned at similar time intervals. Furthermore, we tested if VStr volumetric changes induced by pregnancy could predict VStr functional responses to offspring cues after birth, using a postpartum fMRI paradigm involving pictures of own and other infants. This allowed us to examine—for the first time—whether pregnancy alters VStr volume in a woman's brain, and whether these changes are associated with the infant-related VStr recruitment of the brain's reward circuit that forms a crucial part of the maternal brain.

2. Methods

2.1. Design

The data were acquired by means of a prospective cohort study that was set up to examine the effects of pregnancy on the human brain. For this study, nulliparous women participated in an MRI acquisition before and after the pregnancy of their first child (hereafter referred to as the 'Pre' and 'Post' sessions respectively), allowing us to use each woman's pre-pregnancy brain scan as her individual baseline. A subsample additionally participated in another follow-up session around 2 years after birth (the 'Post +2 years' session). Two groups of nulliparous women were recruited for this study, namely nulliparous women who were planning to try to become pregnant in the near future and nulliparous

women without such plans. Although individuals were recruited separately for these groups based on their intention to become parents in the near future, the final group allocation depended on the actual transition from nulliparity into primiparity in between sessions. The final sample of primiparous women (hereafter referred to as the 'PRG' group) and nulliparous control women (the 'CTR' group) with complete longitudinal datasets is described in the Results section.

The women who were not pregnant between sessions were also investigated longitudinally with a comparable time interval. The participants were recruited via the fertility center Instituto Valenciano de Infertilidad (IVI, Barcelona), by flyers and by word of mouth. Recruitment and data collection for all groups was initiated at the same time. Sixty-five nulliparous women were scanned for the first time point, including 43 women who wanted to become pregnant with their first child. Pre-established exclusion criteria comprised having experienced a previous pregnancy beyond the first trimester, neurological or psychiatric conditions, or a history of substance use disorders as assessed by means of the MINI International Neuropsychiatric Interview, applied by a clinical psychologist (Sheehan et al., 1998).

The study was approved by the local ethics committee (Comitè Ètic d'Investigació Clinica de l'Institut Municipal d'Assistència Sanitària), and written informed consent was obtained from all subjects before their participation in the study. For a more detailed and elaborate description of the sample, recruitment and approach used in this study, see Hoekzema et al. (Hoekzema et al., 2017).

2.2. MRI acquisitions

MRI images for all sessions were obtained in a Philips 3 T scanner. High-resolution anatomical MRI brain scans were acquired using a T1-weighted gradient echo pulse sequence (TR = 8.2 ms, TE = 3.7 ms, NSA = 1, matrix = 256 × 256, FOV = 240 mm, 180 slices, voxel size = 0.94 × 0.94 × 1 mm, no gap, flip angle 8°). The Post MRI session also included an fMRI paradigm (T2*-weighted gradient echo EPI sequence. TR = 3000 ms, TE = 35 ms, matrix = 128 × 128, FOV = 230 mm, 30 slices, voxel size = 1.8 × 1.8 × 4 mm, gap 0.5 mm, flip angle 90°) that examined the new mothers' neural responses to their babies. During the Post MRI session, images of the participant's own baby and of other unknown babies were shown using presentation software (NeuroBehavioral Systems). The images represented cut-out faces on a black background and were matched for size, resolution, brightness and facial expression. For each participant, 28 images of her own baby (14 of each infant in case of twins) and 28 images of another unknown baby were presented in randomized order in an event-related fashion (trial duration 1500 ms, randomized inter-trial interval 750–1250 ms), with an average number of trials of (M ± SD) 72.15 ± 6.64 and 72.40 ± 6.99 for the other baby and own baby conditions respectively. For more details on this paradigm, see Hoekzema et al. (Hoekzema et al., 2017).

Due to an unexpected technical problem, the radio frequency head coil was replaced for some time with another head coil, and 28 scans in total were acquired using the latter coil. There were no significant differences between the groups in the number of scans acquired with this head coil ($\chi^2 = 4.21$, $P = 0.240$). The head coil was introduced as a nuisance covariate in all analyses, except for the analyses involving the Post +2 years session where the coil was matched to the previous session.

Five participants could not be included in the fMRI analyses due to head motion (1 woman), artifacts in the data (2 women), or incomplete data sets (2 women), rendering a sample of 20 primiparous women for this part of the study (age at Pre session: 32.85 ± 4.13).

2.3. Delineation of the VStr

Considering the lack of clear boundaries in signal intensity that hinders the demarcation of the VStr by automated approaches (Patenaude et al., 2011; Loh et al., 2014; Nugent et al., 2013) as well as potential biases resulting from the normalization process, we measured VStr volumes in each subject's native neuroanatomical space using a previously established manual delineation approach (Carmona et al. 2009; Gunduz et al., 2002; Hoekzema et al., 2014; Carmona et al., 2012). This represents a reliable—albeit time-consuming and labor-intensive—method for investigating VStr volume that renders volumes that are in line with histological approaches (Lauer et al., 2001).

Prior to region of interest (ROI) delineation, the anatomical MRI images were oriented into standardized head positions based on AC-PC landmarks using a reorientation script (https://doi.org/10.5281/zenodo.2000727) implemented in Matlab R2017b (www.mathworks.com) and were visually examined to confirm adequate positioning. Visualization and delineation of the images was performed with MRIcroN software (http://www.cabiatl.com/ mricro/mricron). The VStr was manually delineated on coronal slices according to previously established criteria (Carmona et al., 2009; Gunduz et al., 2002; Hoekzema et al., 2014; Carmona et al., 2012). In short, we used the following landmarks: (1) the posterior limit of the VStr was established as the most caudal slice anterior to the anterior commissure; (2) a line perpendicular to the internal capsule demarcated the VStr region, starting at the most inferior and external point of the lateral ventricle; (3) the anterior limit was set as the most rostral slice before the external capsule separated the caudate from the putamen; (4) the paraolfactory gyrus delimitated the inferior and medial boundaries of the VStr. See Fig. 1 for an illustration of the delimitation criteria. The delineation was performed by two raters, who were blind to group and session information. Following the training period, the inter-rater reliability was computed based on 10 repeated regions of interest using intra-class correlation coefficients (ICC: absolute agreement: left VStr: ICC = 0.95; right VStr: ICC = 0.97).Volumes of the individual VStr ROIs were obtained by multiplying the number of voxels included in the ROI by voxel volume. VStr volumes are indicated in cubic millimeters.

2.4. Analyses of VStr volume

Statistical analyses were performed with SPSS 23 (IBM), using repeated-measures general linear models with session (Pre/Post) as the within-subjects factor and group (PRG/CTR) as the between-subjects factor. First, we computed relative VStr volumes expressed as a

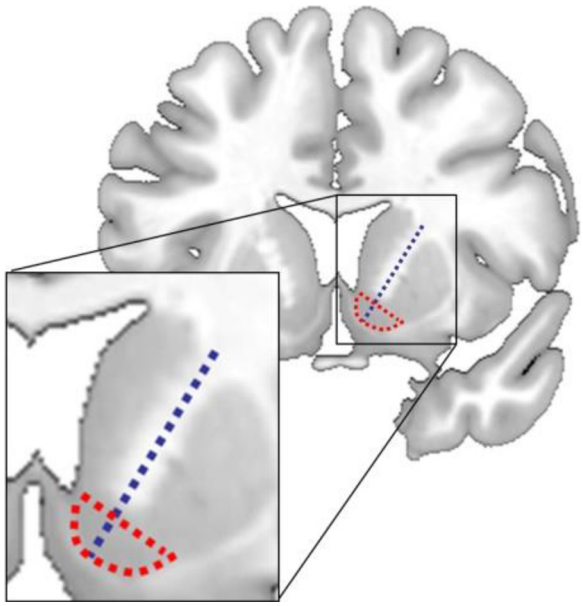

Fig. 1. Illustration of the delineation of the ventral striatum based on the described criteria.

percentage of total brain volume (TBV) (including total grey matter and white matter volume) extracted from FreeSurfer 6.0 (http://surfer.nmr.mgh.harvard.edu) (Fischl et al., 2002). This allowed us to correct for the changes in total brain volume previously associated with pregnancy (Rutherford et al., 2003) that were also observed in this sample (Carmona et al., 2019; Hoekzema et al., 2017). The TBV-corrected measures were used for subsequent analyses, although the results involving the absolute volumes are also provided in the supplementary material. In addition, to examine the specificity of these changes for the ventral part of the striatum, we additionally investigated volume changes in the dorsal striatum. Since the caudate and putamen can be delineated with automatic approaches with a high accuracy based on differences in signal intensity demarcating the boundaries of these structures (Dewey et al., 2010), we extracted caudate and putamen volumes using FreeSurfer and summed these to obtain a measure of the dorsal striatum. Like the VStr volumes, the dorsal striatum measures were corrected for total brain volume and examined using repeated measures general linear models. Left and right volumes were separately examined for all striatal measures since interhemispheric asymmetries have been identified in the dopaminergic system—a highly evolutionarily conserved system (Hoekzema et al. 2010; Perez-Fernandez et al., 2014; Puig et al., 2014; Ryczko et al., 2016)—in rodent striata (Drew et al., 1986; Molochnikov and Cohen, 2014).

To examine the effects of the duration of exposure to postpartum factors (i.e. the time between parturition and the Post scan) on VStr volume, Spearman's correlation analyses were performed with this time interval since this variable was not normally distributed. To further investigate the possibility of postpartum factors affecting VStr volume, we additionally extracted VStr measures from the Post + 2 years session and compared these to those extracted from the early postpartum session using paired samples t-tests. For exploratory purposes, we additionally examined whether the type of delivery (natural delivery versus caesarean section) or breastfeeding status (breastfeeding or not at the time of the session) were associated with distinct changes in VStr volume by means of repeated measures general linear models, although only small samples are available for these exploratory analyses. Results were considered significant when below the statistical threshold of $p < 0.05$.

2.5. Functional MRI analyses

Postpartum neural responses within the VStr were examined by means of an fMRI task that has previously been used to examine mothers' neural responses to their infants (Swain et al., 2007; Swain, 2011). First, the fMRI data were processed and analyzed in normalized space to confirm the activation of this structure in human mothers in response to cues of their infants. Then, each subject's fMRI data was processed in native space to allow extracting individual VStr responses based on the delineated VStr regions. Analyses of the functional MRI data were performed with SPM12 (https://www.fil.ion.ucl.ac.uk/spm/).

2.5.1. Group analyses in MNI space

The functional images were first corrected for differences in slice acquisition timing and realigned to the first volume. Motion parameters were examined in Matlab for the presence of any frame-wise displacements exceeding 3 mm (for translations) or 3° (for rotations). Participants with any head movement that did not meet these criteria were excluded from further analyses (1 woman).The movement parameters were also included as covariates in subsequent analyses. Then, the anatomical images were co-registered to the mean functional image and normalized into MNI (ICBM) space using nonlinear registration (Ashburner and Friston, 2005). Finally, the normalization parameters and a full-width at half-maximum smoothing kernel of 12 mm were applied to the functional images.

At the first level of analysis, general linear models were used to model voxel-wise changes in BOLD response for the conditions of interest, also including the movement parameters extracted during the realignment and regressors based on temporal basis functions. The first-level parameter estimates for the linear contrast 'own baby pictures > other baby pictures' were entered into a second-level model and one-sample *t*-tests were performed to examine whether new mothers show a differential pattern of neural activity in response to pictures of their own or other babies. To examine neural activity within the VStr, ROIs of the left and right VStr drawn on a template image in MRIcroN were applied to this model using Small Volume Correction. The extracted p-values were Family-Wise Error (FWE)-corrected.

2.5.2. Extraction contrast values in native space

To examine whether the changes in VStr volume across pregnancy were associated with this structure's subsequent reactivity to the women's infants, we additionally processed each subject's fMRI data in native space and applied the individually delineated regions of interest to extract estimates of VStr responsivity. This processing pipeline also involved correcting the functional images for slice acquisition timing and realigning the images to the first volume. Subsequently, the co-registration parameters resulting from the co-registration of the mean functional image to the anatomical image were applied to all functional images, followed by the application of a 12 mm smoothing kernel. These functional data were then entered into first-level general linear models.

These native-space models were then loaded into MarsBar 0.44 (http://marsbar.sourceforge.net/), where each person's individual left and right VStr ROIs were applied to the 'own baby pictures > other baby pictures' contrast. The contrast estimates extracted from MarsBar were subsequently entered into Spearman's correlation analyses with the variables representing the change in VStr volume across pregnancy (the Post-Pre VStr volumes) for each hemisphere.

3. Results

3.1. Sample

Table 1 provides demographic and clinical information of the sample. Our final sample consisted of 25 primiparous women (the 'PRG' group) and 20 nulliparous control women (the 'CTR' group) with complete Pre and Post datasets. Unless explicitly stated otherwise, these represent the sample sizes used in the comparisons. The Post session took place on average at 73.56 ± 47.83 days (M ± SD) after parturition. Our sample of primiparous women was additionally asked to participate in another MRI session around 2 years after delivery. Of these 25 women, 11 had not yet experienced a (partial) second pregnancy since the last MRI session and were willing and able to participate in this follow-up session (mean time since birth: M ± SD: 2.32 ± 0.50 years, age at Pre scan: 33.72 ± 3.32 years). There were no statistically significant differences in Pre-to-Post time interval, age or level of education between the PRG and CTR groups. Nonetheless, to control for potential confounding factors, we also repeated our main between-group analyses including these variables (age, educational level, time between Pre and Post session, previous medical conditions, relationship status) as covariates.

3.2. Changes in VStr volume across pregnancy

Repeated measures general linear models were applied to compare the TBV-corrected VStr volume changes across sessions between women who were pregnant between sessions and women who were not. These analyses demonstrated a group (PRG/CTR) x session (Pre/Post) interaction effect for the right VStr and a statistical trend for the left VStr (VStr volumes (%TBV): M ± SD. Left: PRG: Pre: 0.031 ± 0.017, Post: 0.028 ± 0.015. CTR: Pre: 0.030 ± 0.013. Post: 0.031 ± 0.014. $F = 3.353$, $p = 0.074$. Right: PRG: Pre: 0.035 ± 0.016, Post:

Table 1
Sample demographics.

Characteristic	Primiparous women	Nulliparous control women	Between-group differences
Sample Size [nº subjects with complete longitudinal data]			
Pre and Post session	25	20	
Pre, Post and Post +2 session	11	–	
fMRI paradigm	20	–	
Age at Pre [years]			
Mean ± SD	33.36 ± 3.97	31.10 ± 5.63	t = 1.58; p = 0.123
Education [nº subjects]			X^2 = 0.06; p = 0.971
Secondary school	2	2	
College	4	3	
University	19	15	
Pre-Post time [days]			
Mean ± SD	463.52 ± 108.33	413.05 ± 106.86	t = 1.56; p = 0.126
Type of conception			
Natural	9	–	
Assisted	16	–	
Type of parturition			
Vaginal	17	–	
Caesarean section	8	–	
Breastfeeding status			
Breastfeeding	18	–	
Formula	7	–	
Previous medical conditions			
Depression/anxiety	3	1	
Thyroid disorder	3	–	
Anorexia	1	0	
Endometriosis	1	1	
Cholesterol / low blood glucose / hypertension	1	1	
Relationship status [n.º subjects in stable relationship]	24	19	
Mean ± SD [years]	6.49 ± 3.52	5.62 ± 7.17	t = -0.642; p = 0.525

Demographic and clinical information of the sample. There were no statistically significant differences in any of these variables (age, level of education, time between the scans or relationship duration) between the groups. SD = standard deviation, t = t-statistic, p = p-value.

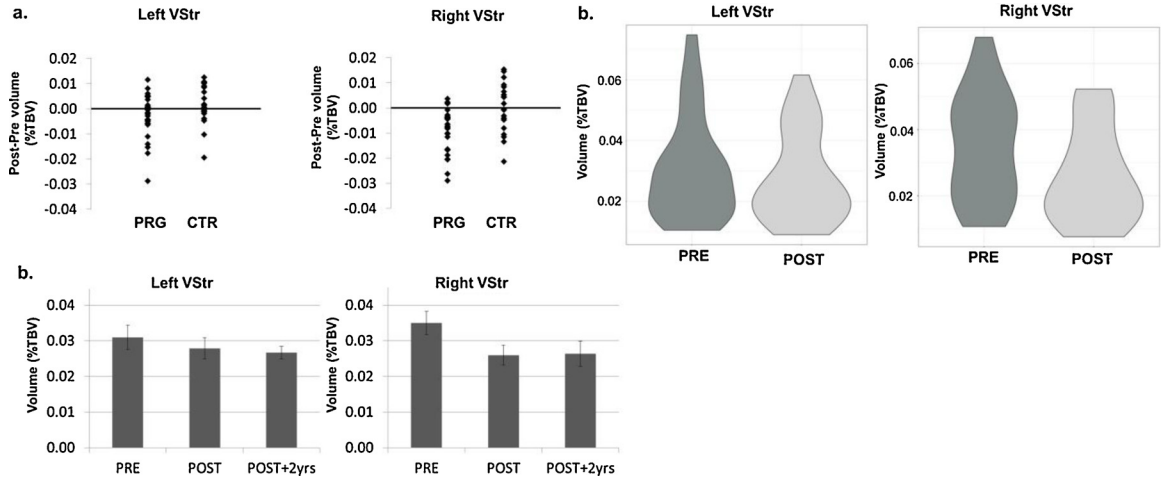

Fig. 2. VStr volumes. a) Scatter plots depicting the changes in TBV-corrected VStr volumes in women who were pregnant between sessions (PRG) and women who were not (CTR). b) Violin plots depicting TBV-corrected VStr volumes for the women who were pregnant between sessions for the pre-conception (PRE) and post-pregnancy (POST) sessions. c) Bar charts depicting TBV-corrected VStr volume (M ± SEM) for each of the three sessions in the PRG group. TBV = Total Brain Volume, PRE = pre-conception baseline session, POST = early postpartum session, POST + 2yrs = postpartum session around 2 years after giving birth.

0.026 ± 0.014. CTR: Pre: 0.029 ± 0.015, Post: 0.029 ± 0.017. F = 9.652, p = 0.003). Paired samples t-tests examining the changes within each of the groups confirmed that the observed effect reflected changes in the PRG sample (Left: t = 1.709, p = 0.100, Right: t = 4.997, p < 0.001) while no changes in volume were observed in the CTR group (Left: t = 0.891, p = 0.384, Right: t = 0.048, p = 0.962). More specifically, the women who were pregnant between the sessions were found to undergo reductions in VStr volume, comprising volume decreases of 7 % and 26 % in terms of the average volume change for the left and right VStr respectively. VStr volumes are depicted in Fig. 2.

In addition, to test if the observed reductions specifically affected the ventral part of the striatum, we examined whether pregnancy is associated with volumetric changes in the dorsal striatum (the part of the striatum comprising the caudate and putamen). Repeated measures general linear models on dorsal striatal volumes revealed no significant group x session interactions (Dorsal striatal volumes (%TBV): M ± SD: Left: PRG: Pre: 0.925 ± 0.0062, Post: 0.915 ± 0.072. CTR: Pre: 0.910 ± 0.097, Post: 0.908 ± 0.0098. F = 0.797, p = 0.377. Right: PRG: Pre: 0.927 ± 0.071, Post: 0.919 ± 0.071. CTR: Pre: 0.916 ± 0.086, Post: 0.910 ± 0.088. F = 0.104, p = 0.749), hereby supporting the relative specificity of the changes for the ventral striatum.

When repeating our main analyses including the demographic and

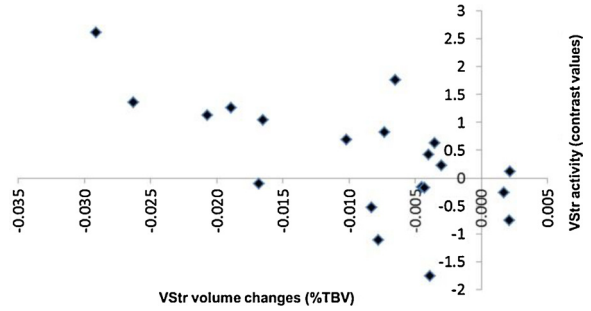

Fig. 3. Correlation between VStr volume changes and postpartum VStr activity. Scatter plot depicting the correlation between right VStr volume changes (total brain volume-corrected) and VStr activation to offspring cues as extracted by applying the individually defined regions of interest to the fMRI data in native space.

clinical variables from Table 1 (age at the Pre session, educational level, time between the Pre and Post sessions, previous medical conditions and relationship status) as confounding factors, we observed highly similar results (Left: $F = 7.034$, $p = 0.012$, Right: $F = 12.953$, $p = 0.001$), although both the left and right VStr now showed significant reductions across pregnancy.

Furthermore, in addition to TBV-corrected volumes, we also examined whether we could observe changes in absolute VStr volumes. These analyses rendered similar results, although significant group x session interaction effects were found for both hemispheres rather than a statistical trend for the left VStr (see Supplementary Table 1).

Finally, to confirm the absence of pre-existing group differences, we also compared VStr volume at the baseline session between the groups. These analyses rendered no significant results, neither for the absolute (Left: $t = 0.161$, $p = 0.873$, Right: $t = 1.145$, $p = 0.258$) nor the TBV-corrected volumes (Left: $t = 0.275$, $p = 0.784$, Right: $t = 1.247$, $p = 0.219$), indicating that there were no significant differences between the groups at baseline (see Supplementary Fig. 1).

Exploratory analyses examining the effects of type of delivery or breastfeeding status on the changes in VStr volume rendered no significant results (all P-values > 0.05, see Supplementary Tables 2–3).

3.3. Postpartum factors

Since the time period between the first and second scan also included a fraction of the early postpartum period, we additionally performed correlation analyses with the duration of exposure to postpartum factors. These analyses indicated no significant associations between changes in VStr volume and the length of the postpartum period included within this time frame for the left ($rs = 0.075$, $p = 0.721$) or the right VStr ($rs = -0.041$, $p = 0.845$).

In addition, to investigate whether changes in VStr volume could be observed across the postpartum period, we additionally delineated the VStr in the subjects who participated in a long-term follow-up session acquired around 2 years after giving birth. Comparisons between the early and late postpartum sessions indicated no further significant changes in VStr volume across this time period, neither for the left VStr nor the right VStr (M ± SD: Left: Post: 0.0298 ± 0.015, Post +2: 0.0267 ± 0.006, $t = 1.033$, $p = 0.326$. Right: Post: 0.0284 ± 0.013, Post +2: 0.0264 ± 0.012, $t = 0.461$, $p = 0.655$), while the volume reductions across pregnancy in the right VStr could also be observed within this subsample (Left VStr: $t = 0.551$, $p = 0.594$, Right VStr: $t = 3.018$, $p = 0.013$).

3.4. Ventro-striatal responses to offspring cues

To examine VStr activity in our sample of mothers in response to visual cues of their babies, we performed group analyses on normalized fMRI data and applied regions of interest of the left and right VStr that were delineated in MNI space. These analyses indicated that both the left and right VStr were strongly activated in response to own infant cues in comparison to other infant cues (Left VStr: MNI coordinates: $x = -6$, $y = 12$, $z = -4$, $t = 5.45$, $p < 0.001$ FWE-corrected. Right VStr: MNI coordinates: $x = 6$, $y = 14$, $z = 0$, $t = 4.90$, $p = 0.002$, $x = 10$, $y = 8$, $z = 0$, $T = 4.27$, $p = 0.005$ FWE-corrected, see Supplementary Fig. 2), hereby supporting the involvement of this structure in the human maternal brain. For completeness, whole-brain results for the 'own baby pictures > other baby pictures' and the reverse contrast are provided in Supplementary Table 4.

3.5. Relation between VStr volume changes and VStr activity

Next, we applied each woman's individual postpartum VStr ROIs to her postpartum fMRI data processed in native space in order to allow extracting a reliable indication of individual VStr activity in response to cues of her infant. The extracted contrast values were then correlated with the individually extracted changes in VStr volume across sessions (the Post-Pre VStr volumes) to examine whether the changes in VStr volumes across pregnancy were associated with a woman's neural response to her baby in this brain region. These analyses indicated that the changes in right VStr volume were negatively associated with this structure's reactivity to own baby cues in the postpartum period ($r = -0.654$, $p = 0$ .002), while no relation was observed between left VStr volumetric changes and left VStr activity ($r = 0.021$, $p = .930$). Our results thus indicate that stronger reductions in right VStr volume across pregnancy are related to a stronger recruitment of this structure in response to the women's infants (see Fig. 3).

4. Discussion

In this paper, we set out to examine whether becoming a mother renders changes in VStr structure that facilitate its responsivity to offspring cues, using a unique pre-conception prospective dataset and a reliable manual neuroanatomical delineation approach. Our results indicate that pregnancy modifies the anatomy of the VStr. More specifically, we found significant reductions in right VStr volume in women who were pregnant between sessions compared to women who were not and a trend for left VStr volume reductions, although it should be noted that significant reductions were also observed in the left VStr when investigating absolute volumes or when including demographic/clinical variables as confounding factors. These effects were evident when controlling for total brain volume and were not observed for the dorsal part of the striatum, indicating that the VStr is specifically affected across this period. When examining the functional activation of the VStr, we found that the structural changes of the VStr across pregnancy are associated with this structure's subsequent responsiveness to the women's infants, with stronger right VStr volume reductions predicting stronger functional activation to offspring cues. These findings thus demonstrate that the VStr is anatomically modified across pregnancy in women, and that these structural changes are associated with this structure's functional responses to the women's babies.

In maternal animals, dopamine is released into the VStr in response to pup-related cues, which is critical for the female's maternal motivation and the adequate expression of caregiving behaviors (Champagne et al., 2004; Fleming et al., 1994). Studies in human mothers have also demonstrated that this structure responds to offspring cues (Atzil et al., 2011; Lorberbaum et al., 2002; Strathearn et al., 2008; Swain, 2011), a finding that was replicated in the present study. The current observations that the VStr undergoes anatomical changes across pregnancy suggest that a woman's neural reward circuit undergoes adaptive changes during this preparatory phase to facilitate the pending transition to motherhood. Accordingly, the observed link between volume reductions across pregnancy and stronger activity in response to cues that are highly relevant for new mothers may point to a

specialization in the reward system that prepares a woman's reward circuit for maximal responsiveness to cues of her infant. It should be noted that these findings do not infer a generalized heightened responsivity of the mesolimbic reward system, but rather a strong reactivity to specific stimuli that are highly relevant to a new mother, i.e. to cues of her infant. In fact, an fMRI study in rats found that the reward circuitry of postpartum females, while being recruited to a greater degree by pup-related cues, was much less responsive to cocaine than in non-mothers (Ferris et al., 2005), suggestive of a specific specialization for contextually relevant stimuli in the brain's reward system.

Volume reductions, as observed in the current study, can signify a process of neurodegeneration, but can also represent a hallmark of neural specialization. For instance, in adolescence, reductions in grey matter volume are regarded as a refinement and specialization of brain circuitry. Grey matter volume decreases across this period are thought to reflect, at least in part, a process of synaptic pruning accompanied by corresponding reductions in metabolic requirements and glial cells as well as increased myelination (Blakemore, 2008; Peper et al., 2011; Sisk and Zehr, 2005; Mills and Tamnes, 2014). Given the apparent similarities between the changes occurring across pregnancy and adolescence, in a previous study we compared the morphometric characteristics of the modifications in the cortical mantle across these two hormone-driven transitional stages of life (Carmona et al., 2019). Interestingly, these analyses revealed a highly similar profile of anatomical alterations, providing further support for the notion that similar neurobiological processes may shape the brain in these periods of extreme hormone changes. Interestingly, a study investigating both cortical grey matter thickness and brain activity in adolescents showed that a thinner cortical mantle was associated with increased brain activity on relevant tasks within these networks (Lu et al., 2009), a finding that is in line with the relation between volume reductions and stronger activity observed in the current study. Considering the strong responsiveness of the VStr to the women's infants as well as the link between volume reductions and greater activity within this structure, the observed findings do not seem to point to a neurodegenerative process but are suggestive of a specialization of the brain's reward system that promotes its reactivity to offspring cues in the maternal brain. Although the cellular mechanisms underlying the observed changes cannot be elucidated based on MRI data, which represents a limitation of neuroimaging studies such as ours, our findings thus provide preliminary support for a functional specialization rather than a loss of function.

In addition to investigating the changes in the VStr across pregnancy, we examined whether we could find indications of postpartum factors affecting VStr anatomy such as sleep loss or interaction with the infant. Correlation analyses with the duration of exposure to postpartum factors rendered no significant results. Furthermore, we compared VStr volumes derived from the sessions in the early postpartum period and those around 2 years after giving birth. In accordance with our correlation results, these analyses revealed no changes in VStr volume across the first two years of motherhood. Taken together, these results suggest that adaptive changes in the reward system primarily occur during pregnancy, presumably driven by the strong endocrine changes associated with this period. Accordingly, studies in various animal species have stressed the role of pregnancy hormones in the emergence of the maternal motivational drive. For instance, a pregnancy-mimicking treatment of estradiol and progesterone was found to induce a preference for pups over food in a conditioned place preference task in female rats (Fleming et al., 1994) and an increased frequency of bar pressing for maternal reinforcement in marmoset monkeys (Pryce et al., 1993). However, it should be noted that it is not possible to discern the factors contributing to the observed changes based on our data. Unfortunately, due to logistic challenges, hormone samples could not be obtained from our participants during pregnancy. This represents an important limitation of this study, as this hampers revealing the mechanisms driving this neuroplasticity. Furthermore, maternal brain changes are likely to represent an interplay between environmental and endocrine factors, and future research monitoring various endocrine and environmental factors in detail is needed to address this limitation and further pinpoint the mediators driving the observed neural plasticity.

When examining our results, it seems that the observed effects are asymmetrical with regard to hemisphere and are generally stronger in the right than the left VStr. For instance, significant changes in VStr volume were only detected in the right hemisphere, while a statistical trend was observed for changes in the left VStr. Likewise, while the VStr was activated bilaterally in response to infant cues, a significant association between VStr volume changes and VStr activity was only observed for the right VStr. Some previous studies investigating the neural responses to own infant cues in comparison to stimuli derived from other infants found only right-lateralized VStr activity (Atzil et al., 2011; Lorberbaum et al., 2002), although another study observed VStr activation only in the left hemisphere (Strathearn et al., 2008). Interestingly, interhemispheric asymmetries have repeatedly been demonstrated in the mesostriatal dopaminergic system (Molochnikov and Cohen, 2014). For instance, female rats have higher dopamine D2 receptor densities in the right striatum (Drew et al., 1986). In humans, indications have also been observed of increased right-sided ventrostriatal dopamine release in humans during rest and in response to rewarding stimuli (Cannon et al., 2009; Martin-Soelch et al., 2011). Functional connectivity analyses of VStr lateralization suggest that the left VStr is more related to internally directed processes, while the right VStr is more strongly involved in externally oriented processes (Zhang et al., 2017), providing a potential framework for interpreting stronger right-sided effects as a mother's reactivity to infants involves a strong focus on external stimuli. However, the presence and significance of a potential hemispheric lateralization in this context remain to be determined.

Taken together, we have shown that becoming a mother entails anatomical alterations in a core structure of the brain's reward system that is known to play a key role in the human and non-human animal maternal brain. Furthermore, these changes were associated with a stronger response within this structure to the women's babies after birth. These results suggest that pregnancy triggers neuroanatomical adaptations within the VStr that prepare a woman's reward circuit to maximally respond to cues of her infant, hereby increasing the incentive value of the newborn.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:10.1016/j.psyneuen.2019.104507.

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