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Oxytocin alters patterns of brain activity and amygdalar connectivity by age during dynamic facial emotion identification

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ABSTRACT

Aging is associated with increased difficulty in facial emotion identification, possibly due to age-related network change. The neuropeptide oxytocin (OT) facilitates emotion identification, but this is understudied in aging. To determine the effects of OT on dynamic facial emotion identification across adulthood, 46 young and 48 older participants self-administered intranasal OT or a placebo in a randomized, double-blind procedure. Older participants were slower and less accurate in identifying emotions. Although there was no behavioral treatment effect, partial least squares analysis supported treatment effects on brain patterns during emotion identification that varied by age and emotion. For young participants, OT altered the processing of sadness and happiness, whereas for older participants, OT only affected the processing of sadness (15.3% covariance, $p = 0.004$). Furthermore, seed partial least squares analysis showed that older participants in the OT group recruited a large-scale amygdalar network that was positively correlated for anger, fear, and happiness, whereas older participants in the placebo group recruited a smaller, negatively correlated network (7% covariance, $p = 0.002$). Advancing the literature, these findings show that OT alters brain activity and amygdalar connectivity by age and emotion.

1. Introduction

Accurately interpreting facial expressions is a crucial skill for successfully navigating the social world (Calder et al., 2003). Aging is robustly associated with increased difficulty in this ability (Ruffman et al., 2008), with negative impacts on social functioning (Noh and Isaacowitz, 2013). The mechanisms underlying age-related deficits in facial emotion identification, however, are still unknown (Ebner and Fischer, 2014), but age-related change in brain connectivity may be at work. Age-related changes in brain connectivity can be adaptive (e.g., increased prefrontal and reduced amygdala recruitment during emotion processing—St Jacques et al., 2010; Ziaei et al., 2017), but they can also be associated with cognitive challenges (e.g., decreases in salience network connectivity—Onoda et al., 2012; reduced suppression of default network—Turner and Spreng, 2015). Understanding the neural underpinnings of age-related changes in emotion processing can help to characterize healthy aging and identify opportunities for intervention.

Intranasal administration of the neuropeptide oxytocin (OT) may be a promising tool for optimizing emotion processes in aging, based on evidence that OT improves the perception of social signals (Kéri and Benedek, 2009), enhances facial emotion identification (Leppanen et al., 2017), and is associated with large-scale network change in young adults (Brodmann et al., 2017). In fact, to date, the effects of OT administration have mostly been examined in young men (Ebner et al., 2013) and only very few studies have investigated OT's effects on task-related functional connectivity with mixed findings (Bethlehem et al., 2013). Recent evidence, however, points to possible age-by-sex variations in OT's effects on emotion processes (Campbell et al., 2014; Ebner et al., 2015) and functional coupling at rest (Ebner et al., 2016).

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The amygdala, in particular, has been identified as a primary region of interest in OT-related connectivity research (Bethlehem et al., 2013) and in research on age-related network change (Sakaki et al., 2013). The amygdala is a hub that is well connected to cortical regions relevant to emotion processing and social cognition (Bickart et al., 2014; Sergerie et al., 2008). Importantly, amygdalar connectivity is impacted by aging and may be a major underlying factor for increased difficulty in emotion identification with age (Huffmeijer et al., 2013; St Jacques et al., 2010). Although the amygdala has been strongly implicated as a mediator of OT's effects, it is still unclear how aging would impact OT's functions in emotion processing (Huffmeijer et al., 2013). Therefore, examining amygdalar connectivity is a promising avenue for synthesizing 2 previously parallel lines of research on age- and OT-related brain network change.

To address this gap in the literature, the present study examined age-related differences in behavior, whole-brain patterns, and amygdalar functional connectivity during a dynamic facial emotion identification task, and in this context, the role of intranasal OT administration on altering behavior and brain patterns was considered. We predicted the following:

(1) Better identification of, particularly negative, facial emotions in young than older participants (Ruffman et al., 2008).
(2) Better facial emotion identification in the OT than the placebo (P) group, particularly among older individuals (Campbell et al., 2014; Leppanen et al., 2017).
(3) Greater recruitment of anterior and midline regions, consistent with observed default network activity during facial emotion identification (Martins and Mather, 2016), in older than young participants.
(4) Greater recruitment of regions implicated in dynamic facial emotion identification (Kessler et al., 2011; LaBar et al., 2003) and the salience network (e.g., anterior insula [AI] and anterior cingulate cortex [ACC]) in the OT than the P group across age groups (Uddin, 2015).
(5) Age-specific patterns of amygdalar connectivity during dynamic facial emotion identification (i.e., an amygdalar network connected to more frontal regions in older participants vs. an amygdalar network connected to more posterior regions in young participants) (Huffmeijer et al., 2013; St Jacques et al., 2010).
(6) OT-related change in functional connectivity, compared with placebo (P), in these amygdalar networks across age groups and emotion (sadness, anger, fear, happiness).

2. Material and methods

2.1. Participants

The behavioral sample comprised 48 young (M = 22.4 years, SD = 3.0, 18–31 years, 48% female) and 54 older (M = 71.2 years, SD = 4.9, 63–81 years, 56% female) generally healthy adults, of which 26 young (46% female) and 27 older (56% female) were randomly assigned to the OT group and 22 young (50% female) and 27 older (56% female) to the P group. Eight participants were excluded from fMRI analysis for corrupted images, excessive head motion, outlying brain scores, or missing data. Thus, the fMRI sample comprised 46 young (M = 22.5 years, SD = 3.1, 18–31 years, 47.8% female) and 48 older (M = 71.1 years, SD = 5.2, 63–81 years, 56.3% female) adults, of which 26 young (46% female) and 24 older (50% female) were assigned to the OT group and 20 young (50% female) and 24 older (63% female) to the P group.

All participants were white, English-speaking with no history of neurological or psychiatric disorder and with perfect or corrected vision. All older participants scored ≥30 on the Telephone Interview for Cognitive Status (Brandt et al., 1988). Age and treatment group differences in sample-descriptive data were assessed separately using one-way between-subjects analysis of variance (see Table 1 in Supplementary Material for details on sample-descriptive data). In particular, age groups were comparable in education level and subjective ratings of physical and mental health but differed in sensorimotor processing speed (Digit Symbol Substitution Test; Wechsler, 1981) [$F(1,100) = 110.0$, $p < 0.05$, $\eta_p^2 = 0.5$] and short-term verbal learning memory (Rey Auditory Verbal Learning Test; Rey, 1964) [$F(1,100) = 14.9$, $p < 0.05$, $\eta_p^2 = 0.1$] in line with the literature (Hoyer et al., 2004; Vakil and Blachstein, 1997). Both age groups reported comparable pretreatment negative mood, but older (M = 3.5, SD = 0.6) compared with young (M = 2.8, SD = 0.7) participants reported higher positive mood (Positive Affect Negative Affect Schedule; Watson et al., 1988) [$F(1,100) = 29.0$, $p < 0.05$, $\eta_p^2 = 0.2$]. The treatment groups did not differ in any of these measures.

2.2. Procedure

This study used a randomized, double-blind, between-group design that comprised an initial phone call to determine study eligibility (~30 minutes), an in-person screening session (~45 minutes), and an in-person full session (~3 hours). Only measures relevant to the present analyses are reported (Ebner et al., 2015, 2016, 2019).

All participants provided informed consent before enrollment. Participants were instructed to stay hydrated and to abstain from substance use and caffeine for 24 hours and to abstain from food, exercise, and sexual activity at least 2 hours before the sessions. All in-person sessions took place at ~8:00 AM. This study was approved by the University Institutional Review Board (IRB#39–2013) and preregistered with ClinicalTrials.gov (NCT01823146).

During the in-person screening session, participants completed an intake interview on behavior from the past 24 hours, short questionnaires, the Digit Symbol Substitution Test, and the Rey Auditory Verbal Learning Test. Saliva and blood sampling was conducted along with a health review by a clinician. During the in-person full session, participants underwent MRI safety determination. Participants completed another intake interview, the Positive Affect Negative Affect Schedule, and underwent saliva sampling. Following recommendations for the standardized administration of intranasal OT (Guastella et al., 2013), participants self-administered 24 international units (IU; one puff per nostril) of OT or P, which contained the same ingredients as the OT spray except for the OT. Compounding, dispensing, and randomization were overseen by the dispensing pharmacy.

Before scanning, participants received instructions on scanning procedure and the tasks, including practice runs, and were settled into the 3T MRI scanner ~45 minutes after self-administration. Participants underwent anatomical image acquisition followed by functional image acquisition across 4 tasks (see also Ebner et al., 2016). Participants engaged in the dynamic facial emotion identification task ~90 minutes after self-administration and completed, outside the scanner, social and affective questionnaires plus a post-event questionnaire about their experience with the spray and scanner, before being debriefed and compensated. Approximately 1 week later, participants received a follow-up call to assess any side effects of the spray. No consistent or adverse side effects were reported.

2.3. Dynamic facial emotion identification task

This task was modeled after Lischke et al. (2012) for fMRI use in Experiment Builder (http://www.sr-research.com/eb.html). Twelve high-quality images of young adults (6 males and 6 females) were

chosen from the FACES database (Ebner et al., 2010) with neutral expressions and 4 corresponding emotional expressions: sadness, anger, fear, and happiness. Following a jittered fixation cross ranging between 5, 7, and 9 seconds ($M = 7$ seconds), a neutral face was presented that morphed into an emotive face at 5% increments of emotion intensity per image. Each image in a set for a specific facial identity and emotion was presented for 1 second (21 images per set). Participants were asked to identify, as quickly and as accurately as possible, the emotion presented via a button press. A 4-button response box (Mag Concepts Inc) that rested on the participants' abdomen during the task in the scanner was used for emotion identification. The assignment of fingers to emotions was kept consistent across participants (sadness, index; anger, middle; fear, ring; and happiness, pinky). The emotion continued to develop after a response was made. No feedback was provided.

Stimuli were counterbalanced by facial emotion, sex, and identity across 4 lists. Facial identities were presented in the same order for each list with no more than 2 presentations of the same sex in a row. Each identity was used once before showing the same identity again with a different emotion. No more than 2 faces with the same emotion were repeated in a row, and every emotion was presented 3 times per run (16 faces per run, 7.7 minutes per run, 3 runs per session).

2.4. Image acquisition and preprocessing

A 3T Philips Achieva MR scanner (Philips Medical Systems; Best, The Netherlands) acquired images using a 32-channel head coil. Whole-brain high-resolution 3-dimensional T1-weighted anatomical reference images were acquired using an MP-RAGE sequence (sagittal plane, 170 slices, FOV 240 $\times$ 240 mm^2; 1 mm^3 isotropic voxels). Functional images were obtained using whole-head echo-planar imaging and a single-shot gradient echo (38 interleaved slices, TR 2 seconds, TE 30 ms, FOV 252 $\times$ 252 mm^2, flip angle 90°, in-plane resolution of 3.15 $\times$ 3.15 mm^2, slice thickness 3.5 mm, no skip). A total of 234 volumes per participant were acquired for each of the 3 runs.

Data preprocessing was conducted using the CONN default preprocessing pipeline for volume-based analysis to MNI space (Whitfield-Gabrieli and Nieto-Castanon, 2012). This included functional realignment and unwarping, slice-timing correction, structural segmentation and normalization, functional normalization, outlier detection, and smoothing. Functional images were normalized into standard stereotaxic MNI space with a target voxel size of 2 mm and smoothed with an 8 mm Gaussian kernel. Regression of white matter and cerebrospinal fluid signal was conducted using aCompCor (Behzadi et al., 2007). Motion artifacts greater than 2 mm were coded as a separate variable by ArtRepair (Mazaika et al., 2009) and removed for individual time series.

2.5. Behavioral analysis

To determine age and treatment effects on behavioral performance in dynamic facial emotion identification, 2 separate repeated-measures analysis of variances on reaction time (ms for correct trials) and accuracy (percent correct trials), respectively, were conducted with age (young vs. older) and treatment (OT vs. P) as the between-subject variables and facial emotion as the within-subject variable. The significance threshold for the behavioral results was set to $p < 0.05$.

2.6. Task partial least squares analysis

To determine OT-related brain patterns associated with dynamic facial emotion identification by age and treatment, event-related mean-centered task partial least squares (PLS; Type 2, which removes the grand mean for all participants and conditions) was implemented. PLS is a model-free, multivariate, relational measure of patterns of activation and connectivity, which allowed us to examine OT-related networks over time (McIntosh and Lobaugh, 2004). This data-driven approach determines orthogonal whole-brain patterns of activity as latent variables (LVs), which optimally relate blood-oxygen level–dependent signal with the experimental design. However, unlike principal component analysis, the number of LVs is constrained by experimental conditions. Unlike univariate analysis, PLS detects brain-wide systems that covary with the experimental design in a single step (i.e., decomposition and resampling are concurrently applied to all voxels). Therefore, multiple comparisons correction is not required (McIntosh et al., 1996; McIntosh and Lobaugh, 2004).

For each trial, activity for each voxel was averaged across runs for each condition and normalized to activity at trial onset. The data matrix was expressed as a voxel-by-voxel deviation from the grand mean across the entire experiment. This matrix was analyzed with singular value decomposition to derive optimal effects in the data. The results provide a set of regions wherein activity was reliably related to task conditions and groups for each LV.

Each voxel is given a singular value weight (i.e., a salience), which is proportional to the covariance of activity with the task contrast on each LV. Multiplying the salience by the blood-oxygen level–dependent signal value in that voxel and summing the product across all voxels gives a composite brain activity score for each participant on a given LV. These scores are used to examine similarities and differences in activity across conditions, as greater activity in regions with positive (or negative) weights on an LV will yield positive (or negative) mean scores for a given condition.

The significance of each LV ($p < 0.01$) and their corresponding patterns was assessed through permutation testing (500 permutations) by randomly reassigning the order of conditions for each participant. PLS is recalculated for each permutation sample, and the frequency with which the permuted singular value exceeds the observed singular values is determined and expressed as a probability. In an independent step, the reliability of the saliences for voxels across participants, characterizing each pattern identified by an LV, was determined by iterative bootstrap resampling with replacement (100 iterations) to estimate the standard errors for each voxel. Confidence intervals (CIs) (95%) for the mean composite brain activity score in each condition and group were calculated from the bootstrap, and differences in activity between conditions were determined via a lack of overlap in these CIs.

We limited the time window for our brain analyses to the first 8 lags (1 lag or 1 TR), which corresponded to 16,000 ms after trial onset, to capture the temporal variation in emotion processing across task conditions and groups. Our interpretations of brain activity were drawn from the lags that maximally dissociated conditions and groups, which varied per LV.

Clusters larger than 10 voxels with a ratio of the salience to the bootstrap standard error values (i.e., bootstrap ratio [BSR]) greater than ± 2.58 ($p < 0.01$) were considered reliable (Krishnan et al., 2011) and presented in the brain maps (Figs. 1–4) using Caret v5.65 (Van Essen, 2005). We defined the local maximum for each cluster as the voxel with a BSR higher than any other voxel in a 2-cm cube centered on that voxel. Regions were defined from peak MNI coordinates using Neurosynth (Yarkoni et al., 2011) and MRIcron (Rorden and Brett, 2000).

2.7. Seed PLS analysis

Seed PLS was conducted to determine if there were age and treatment differences in amygdalar connectivity during dynamic

facial emotion identification and if connectivity varied by emotion. Seed PLS investigates the relationship between a seed region of interest and the whole-brain voxel response (Krishnan et al., 2011). The a priori functional loci were theoretically backed (Bethlehem et al., 2013; Huffmeijer et al., 2013) and were determined via the task PLS analysis from a peak voxel corresponding to the left amygdala (MNI = −28, −6, −10; lag 6; BSR = −5.73; neighborhood size = 1) (Tzourio-Mazoyer et al., 2002). Amygdala seed values were correlated with activity in all voxels across participants. This correlation matrix was then analyzed with singular value decomposition, assessed for statistical significance by permutation testing, and for reliability by bootstrap resampling, as described previously.

3. Behavioral results

3.1. Reaction time

The average reaction time across emotion and treatment was 8764 ms (SD = 1651) in young participants and 10,202 ms (SD = 2537) in older participants. There were significant main effects for age [$F(1, 98) = 14.6$, $p < 0.001$, $\eta_p^2 = 0.1$] and facial emotion [$F(2.8, 270.0) = 190.5$, $p < 0.001$, $\eta_p^2 = 0.7$] and a significant age-by-emotion interaction [$F(2.8, 270.0) = 5.1$, $p = 0.02$, $\eta_p^2 = 0.1$]. Older participants (sadness: M = 12,311 ms, SD = 3020; anger: M = 10,783 ms, SD = 3297; fear: M = 10,825 ms, SD = 2841) were slower than young participants (sadness: M = 10,243 ms, SD = 2098; anger: M = 8935 ms, SD = 2002; fear: M = 9006 ms, SD = 1717) in correctly identifying dynamic facial emotions for all emotions except for happiness, for which the reaction time difference was only marginally significant between young and older participants (p = 0.06). No other effects were significant.

3.2. Accuracy

There were significant main effects for age [$F(1, 98) = 22.8$, $p < 0.001$, $\eta_p^2 = 0.2$] and facial emotion [$F(3, 294) = 30.4$, $p < 0.001$, $\eta_p^2 = 0.2$] and a significant age-by-emotion interaction [$F(3, 294) = 6.1$, $p < 0.001$, $\eta_p^2 = 0.1$]. Older participants (sadness: M = 75.5%, SD = 23.1; anger: M = 77.6%, SD = 21.1; fear: M = 79.6%, SD = 20.1; happiness: M = 91.4%, SD = 15.5) were less accurate than young participants (sadness: M = 88.9%, SD = 9.6; anger: M = 93.8%, SD = 9.5; fear: M = 94.8%, SD = 8.4; happiness: M = 97.4%, SD = 5.5) across all emotions. Difference scores between young and older participants were smaller for happiness (6.0%) than for each negative emotion (sadness: 13.4%; anger: 16.1%; fear: 15.2%). Both young (M = 97.4%, SD = 5.5) and older (M = 91.4%, SD = 15.5) participants had the least difficulty identifying happiness, and both young (M = 88.9%, SD = 9.6) and older (M = 75.5%, SD = 23.1) participants had the most difficulty accurately identifying sadness. No other effects were significant. Table 2 in Supplementary Material presents details on the behavioral results.

4. Task PLS results

Task PLS analysis of the 4 age-by-treatment groups (Young OT, Young P, Older OT, and Older P) and the 4 task conditions (sadness, anger, fear, and happiness) resulted in 2 significant LVs representing multivariate dissociations of brain patterns relating to dynamic facial emotion identification. The first significant LV accounted for 31.4% covariance (p = 0.002) and showed an age-driven dissociation. As depicted in Fig. 1, the age groups recruited 2 distinct patterns involved in the processing of all facial emotions. In particular, young participants recruited a pattern including the AI, cerebellum, inferior frontal gyrus, postcentral gyrus, precentral gyrus, superior parietal lobule, temporoparietal junction, ACC, and thalamus (cool regions). In contrast, older participants recruited the precentral gyrus, ventromedial prefrontal cortex, medial temporal lobe, medial prefrontal cortex (mPFC), middle temporal cortex, and lateral cortex (warm regions) (see Table 3 in Supplementary Material for peak activations from these regions). Although young participants in the OT and P groups recruited cool regions similarly across all emotions (CIs overlapping), older participants in the OT than the P group showed lower recruitment in the warm regions for the processing of sadness.

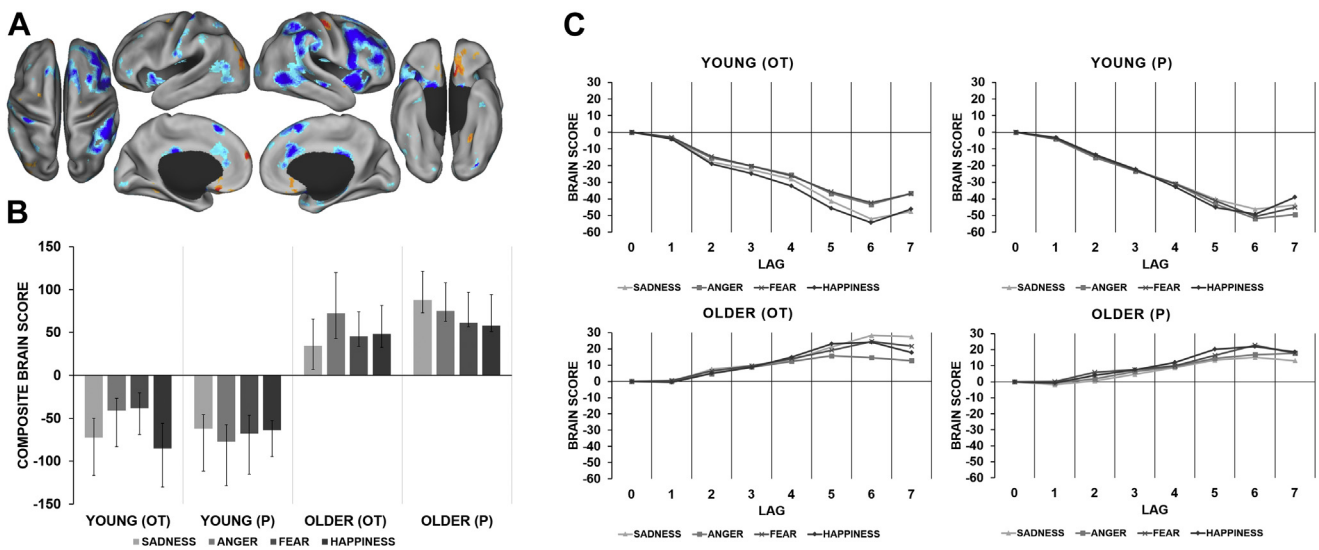

Fig. 1. Age-specific brain patterns relating to dynamic emotion identification. (A) Functional activation map with warm colors that correspond to the brain pattern recruited by older participants and cool colors that correspond to the brain pattern recruited by young participants. This brain pattern was mapped at the time point of greatest temporal dissociation between age groups (lag 6). (B) Composite brain score plot depicting the contrast in pattern recruitment for each condition and group (95% confidence interval). (C) Temporal brain score plot showing brain scores corresponding to each lag in the designated time window after trial onset. Abbreviations: OT, oxytocin; P, placebo. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

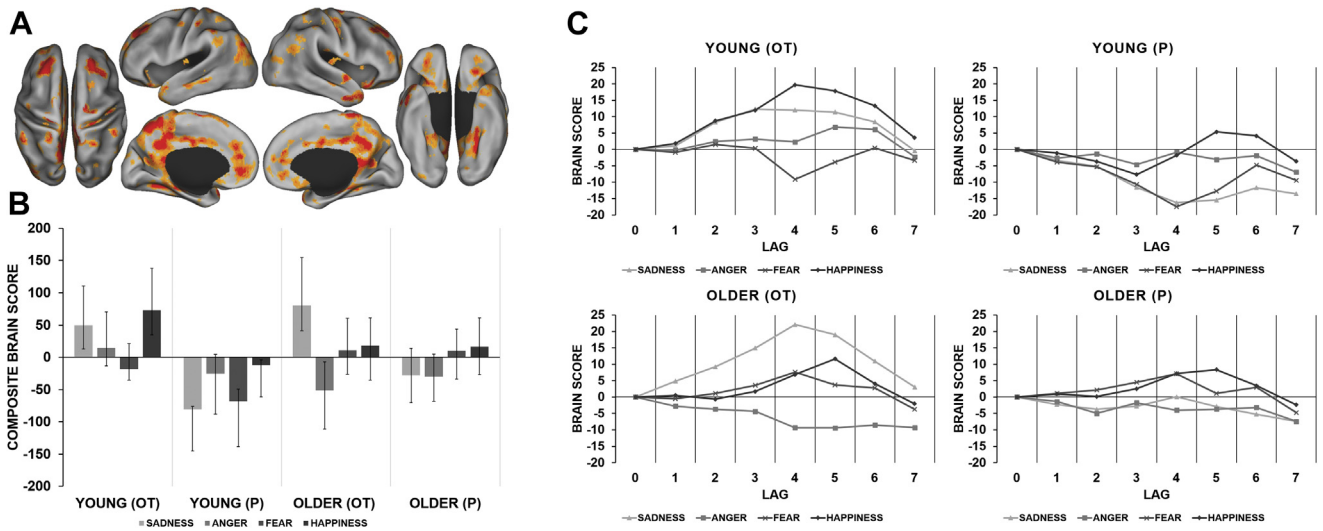

Fig. 2. Treatment- and emotion-specific brain pattern relating to dynamic facial emotion identification. (A) Functional activation map with warm colors that correspond to the brain pattern recruited by young participants in the OT group for sadness and happiness and older participants in the OT group for sadness only. This brain pattern was mapped at the time point of greatest temporal dissociation between treatment groups (lag 4). (B) Composite brain score plot depicting the contrast in pattern recruitment for each condition and group (95% confidence interval). (C) Temporal brain score plot showing brain scores corresponding to each lag in the designated time window after trial onset. Abbreviations: OT, oxytocin; P, placebo. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

The second significant LV accounted for 15.3% covariance ($p = 0.004$) and showed an OT-related brain pattern recruited by both age groups for specific emotions. As presented in Fig. 2, this pattern was recruited by young participants in the OT group (compared with P) for both happiness and sadness and by older participants in the OT group (compared with P) for sadness only. This treatment-by-emotion–specific pattern included the superior frontal cortex, postcentral gyrus, fusiform gyrus, temporal pole, inferior temporal gyrus, superior temporal sulcus, middle temporal gyrus, posterior insula, parahippocampal gyrus, cerebellum, superior occipital cortex, and temporoparietal junction (see Table 4 in Supplementary Material for peak activations from these regions).

5. Seed PLS results

Seed PLS analysis determined 2 significant LVs associated with amygdalar connectivity relating to dynamic facial emotion identification. The first significant seed LV explained 56.0% covariance ($p = 0.002$). As depicted in Fig. 3, much of the covariance in the data was explained by a robust amygdalar network for both age groups. This amygdalar network included other amygdalar clusters, cerebellum, inferior temporal gyrus, primary visual cortex, inferior occipital cortex, and the ACC (see Table 5 in Supplementary Material for peak activations from these regions). This pattern applied to all emotions in young participants but was only specific to anger, fear, and happiness in older participants (CIs crossing zero for sadness).

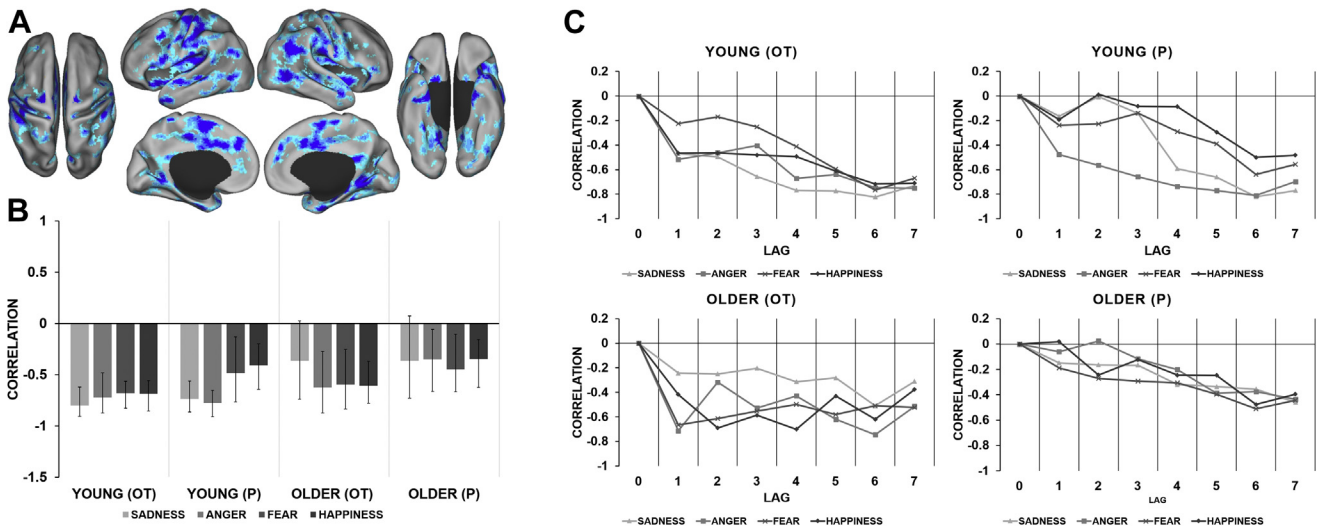

Fig. 3. Amygdalar network recruited by both age groups for all dynamic facial emotions. (A) Functional connectivity map with cool colors that correspond to a large-scale amygdalar network was recruited by both young and older participants for all emotions. This network was mapped at the time point of greatest temporal dissociation between age groups (lag 2). (B) Composite correlation plot depicting amygdalar connectivity for each condition and group (95% CI). Note that this network was not reliable for older participants in response to sadness due to CIs crossing zero. (C) Temporal correlation plot showing correlations corresponding to each lag in the designated time window after trial onset. There were several timepoints of greatest temporal dissociation between age groups, which varied by emotion (lag 2: happiness and fear, lag 4: anger); however, this network was mapped at lag 2 only as this widespread pattern persisted for the entire time window. Abbreviations: CI, confidence interval; OT, oxytocin; P, placebo. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

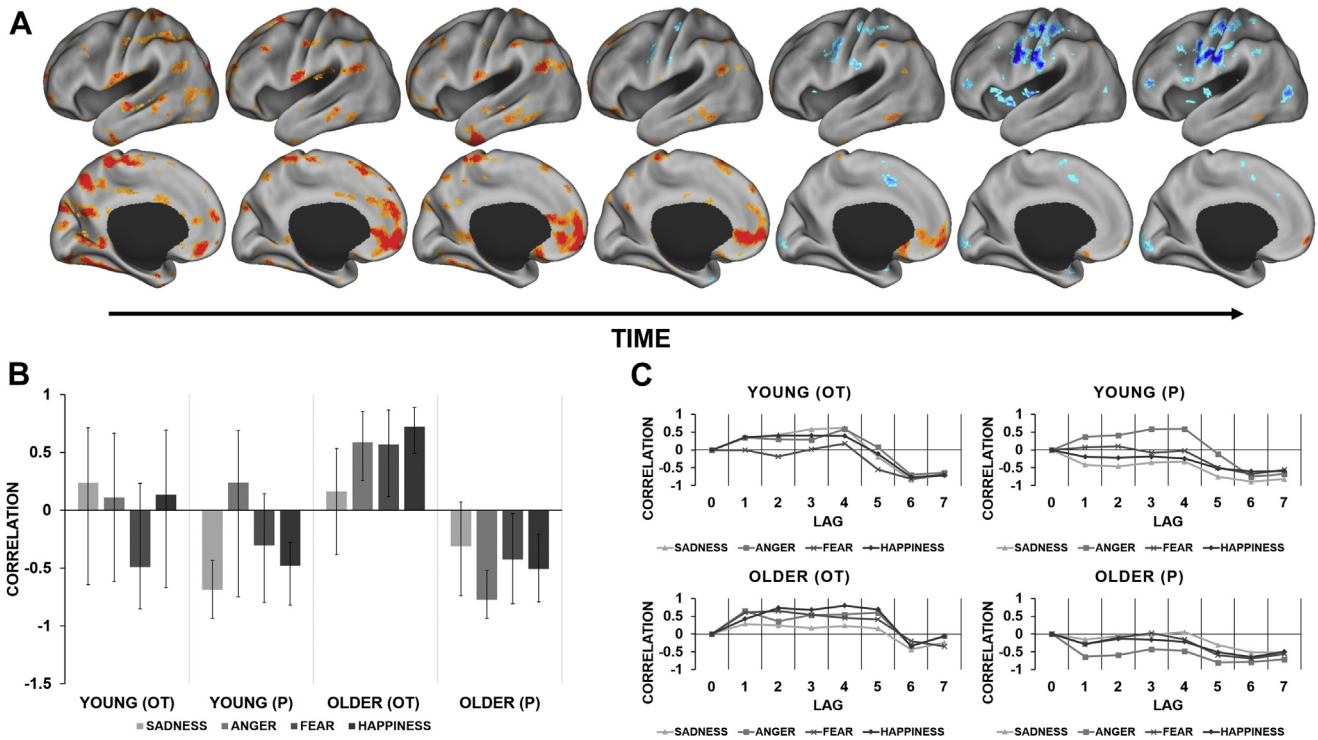

Fig. 4. Emotion-specific amygdalar networks for older participants that varied by OT versus P. (A) Functional connectivity maps (1 map per lag in medial and lateral view) representing the temporal unfolding of 2 distinct age- and emotion-specific amygdala networks further distinguished by treatment (OT vs. P). Warm colors correspond to an amygdala network recruited by older participants in the OT group for anger, fear, and happiness that emerged early in the task. Cool colors correspond to an amygdala network recruited by older participants in the P group for these same emotions that emerged later in the task. (B) Composite correlation plot depicting amygdalar connectivity for each condition and group (95% CI). Note that these networks were not reliable for older participants in response to sadness due to CIs crossing zero. (C) Temporal correlation plot that shows correlations corresponding to each lag in the designated time window after trial onset. Abbreviations: CI, confidence interval; OT, oxytocin; P, placebo. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

The second significant seed LV explained 7.0% covariance ($p = 0.002$) and represented a multivariate dissociation in amygdalar connectivity that was specific to age, treatment, and emotion. Fig. 4 depicts 2 distinct amygdalar networks recruited by older participants that unfolded at different timepoints during the task. In particular, older participants in the OT group recruited a large-scale network early in the task that was positively correlated with the amygdala in response to anger, fear, and happiness (warm regions). This network included the mPFC, subgenual anterior cingulate gyrus, superior frontal gyrus, corpus callosum, superior temporal sulcus, hippocampus, caudate, superior frontal gyrus, cerebellum, angular gyrus, parahippocampal gyrus, inferior temporal gyrus, and cuneus. In contrast, older participants in the P group recruited a smaller network later in the task that was negatively correlated with the amygdala in response to anger, fear, and happiness, which included the putamen and posterior parietal lobule (cool regions). Of note, both networks included overlapping regions such as the precentral and postcentral gyrus (see Table 6 in Supplementary Material for peak activations from these regions). These networks were not reliable for older participants in response to sadness and among young participants (CIs crossing zero). Fig. 4A and C shows the change in network recruitment due to OT administration in lags 4 and 5. As evidenced by the composite brain score plot (Fig. 4B), this dissociation was reliable only when comparing older participants in the OT versus the P group.

6. Discussion

Integrating parallel lines of research on age- and OT-related brain network change, the present study (1) identified brain activity and connectivity patterns underlying dynamic facial emotion identification across adulthood and (2) determined the effects of intranasal OT administration on brain function and behavior related to emotion processing in aging. We found age-related differences persisted for dynamic (compared to static) facial emotion identification in terms of behavior and whole-brain pattern recruitment but not in amygdalar connectivity. Second, although we observed no behavioral treatment effect, OT altered brain activity and amygdalar connectivity by age and emotion. These novel findings will be discussed in detail next.

6.1. Older adults were slower and less accurate in dynamic facial emotion identification than young adults, but OT did not moderate this effect

As expected, older participants were slower and less accurate in dynamic facial emotion identification than young participants. These effects were pronounced for negative compared with positive emotions. These findings corroborate previous results with static emotions (Ebner and Johnson, 2009) and are among an emerging literature suggesting comparable age effects for dynamic and static facial emotions (Di Domenico et al., 2015).

However, we did not observe behavioral effects of OT administration on emotion identification. Although some previous studies suggest that intranasal OT improves emotion identification (Leppanen et al., 2017; Shahrestani et al., 2013), other studies reported null effects of OT on emotion identification–related behavior in young (Chen et al., 2015; Lischke et al., 2012) and older (Grainger et al., 2018) adults, in line with the present study's findings. For example, Lischke et al. (2012) found that OT increased

accuracy for fear but not for happiness, anger, or sadness in young men (OT: $n = 23$, P: $n = 24$). Similarly, we did not find an OT-related behavioral increase in accuracy for these emotions, including fear, in young and older adults.

This lack of OT-related behavioral effects may be due to several factors. For example, the present study only assessed accuracy and reaction time, whereas other behavioral measures could be more sensitive to OT administration. Future studies may benefit from using behavioral measures such as eye- or mouse-tracking and by presenting finer-grained intensity levels of emotional stimuli and/or faster developing, more naturalistic facial emotion displays (Holland et al., 2018). Furthermore, tasks that incorporate naturalistic presentations of social emotions (e.g., pride, shame, jealousy) (Adolphs, 2002) or other visual and/or auditory emotional cues (Bänziger et al., 2012; Martinez et al., 2016) may generate greater interindividual variability and may be more sensitive to OT's effects.

It is also possible that high overall accuracy in the present study resulted in limited interindividual variability, reducing the likelihood to detect OT's effects on dynamic facial emotion identification—related behavior. A crossover study in 203 men by Chen et al. (2015), using a similar task as in the present study, found that accuracy was near ceiling across participants ($M = 88.0\%$, $SD = 9.0\%$) and found no significant main effect of OT on reaction time. Given the lack of behavioral effects observed in multiple studies combined with evidence that OT facilitates early attention to social stimuli (Shamay-Tsoory and Abu-Akel, 2016), it is possible that OT impacts emotion identification at very early stages of facial processing. Thus, future studies incorporating methods that consider temporal variability (e.g., ERP, EEG) may be promising to elucidate the underlying processes of OT's effects on face and emotion perception.

Moreover, although we considered age and treatment as between-group variables in the present study, we did not consider other, possibly relevant, interindividual difference variables such as variations in endogenous OT levels and their interaction with exogenous OT (Chen et al., 2015). Attention to interindividual differences is especially important for future research on OT's effects in older adults, given the diverse healthy or pathological aging trajectories individuals follow (Jesso et al., 2011) and the currently limited understanding of the OT system in human aging (Ebner et al., 2013).

Also, a growing literature suggests that sex constitutes an important moderator of OT's effects, as gonadal hormones interact with OT (Ebner et al., 2015; Macdonald, 2013; Macdonald and Feifel, 2013). For example, in young men, intranasal OT reduced amygdala activity in response to unpleasant social (Gamer et al., 2010) and emotional stimuli (Domes et al., 2007; Kirsch et al., 2005), whereas intranasal OT increased activity in the amygdala in response to fear in young women (Domes et al., 2010) (see also Bethlehem et al., 2013; Domes et al., 2007; Lischke et al., 2012 for more on sexually dimorphic effects). To date, only very few studies have examined the effects of intranasal OT on social cognition with consideration of age and sex (Campbell et al., 2014; Ebner et al., 2015, 2016; Grainger et al., 2018), and future systematic work on this topic is needed. Campbell et al. found that older men who self-administered OT (compared with P) showed improved facial emotion identification. Similarly, in older men, OT (compared with P) was associated with enhanced awareness of their own emotions (Ebner et al., 2015). Intranasal OT also increased amygdala-mPFC coupling at rest for young women and trend-wise for older men but not in the other age-by-sex subgroups (Ebner et al., 2016). The present study was not sufficiently powered to consider sex as an additional design factor (over and above age, treatment, and facial emotion), which will have to be systematically addressed in future extensions of the current work.

Furthermore, the present study's sample size may have resulted in limited statistical power to detect significant OT-related behavioral effects. A recent meta-analysis, published after the present study's closure, recommends that behavioral studies on OT and emotion identification should have at least 64 participants in each group to reliably assess differences between 2 groups, such as OT versus P (effect size ≥ 0.5) (Leppanen et al., 2017). Our treatment groups were slightly under this size (OT: $n = 53$, P: $n = 49$). Other studies using a similar task were also limited in terms of only focusing on OT's effects in 1 sex and/or in small samples (Chen et al., 2015; Di Simplicio et al., 2009; Kim et al., 2015; Lischke et al., 2012). Thus, larger sample sizes in future extensions of this work are needed to not only drive neurophysiological responses to stimuli but also to distinguish OT-related behavioral responses.

6.2. OT altered brain patterns and amygdalar connectivity by age during dynamic facial emotion identification

Our findings regarding brain activity patterns and amygdalar connectivity were largely in line with our predictions. Young participants recruited the AI and ACC of the salience network during dynamic facial emotion identification. In contrast, older participants recruited more anterior and midline regions including the mPFC, a major node of the default network. These findings support age-related differences in brain activity patterns during dynamic emotion processing, which qualify previous work conducted in young and older adults using static facial emotions (Keightley et al., 2007; Ziaei et al., 2016). Also, although both age groups recruited frontal and temporoparietal regions during the task (Kessler et al., 2011; LaBar et al., 2003), amygdala activation only emerged as a significant node in the young adult brain pattern. This finding is in line with decreased amygdala and increased prefrontal recruitment during emotion processing in older adults (Keightley et al., 2007; but see Ziaei et al., 2017).

Regarding OT effects, we found that OT altered a brain pattern associated with the processing of sadness and happiness in young participants yet only for sadness in older participants. In contrast, there were no treatment-related effects in brain activity for anger and fear in either of the age groups. These results may reflect OT's attention-orienting role in prompting emotion-specific prosocial responses to stimuli (e.g., sadness, empathic response; happiness, approach response) (Theodoridou et al., 2013; but see Tollenaar et al., 2013). Furthermore, the finding that OT altered brain activity only for sadness in the older group versus happiness and sadness in the young group could be linked to individual differences in the endogenous OT system. Previous research has shown that a specific polymorphism of the OT receptor gene (*OXTR*; AA compared with GA/GG carriers of *OXTR* rs237887) was associated with increased activity in the ACC and reduced reaction time for the identification of happiness in older adults. GA/GG carriers may leverage the ACC to accurately identify positive emotions (Ebner et al., 2013). A combined neural, behavioral, and genetic approach that examines interactions between intranasal OT and the OT system may elucidate individual differences in emotion processing in aging.

The present study's seed PLS analysis showed a robust amygdalar network related to dynamic facial emotion identification in both age groups, suggesting that amygdalar connectivity for the identification of dynamic facial emotions may be preserved in aging. This finding contrasts with previous work on static emotion processing that showed age-related differences in amygdalar connectivity (Keightley et al., 2007; St Jacques et al., 2010). Follow-up studies will allow determination of age-related similarities and differences in connectivity relating to naturalistic (i.e., dynamic) emotion processing. Directly correlating behavioral performance or

other relevant measures to task-related or resting-state networks will also further advance the characterization of individual socio-emotional aging trajectories.

OT administration was associated with a more widespread amygdalar network in older (but not young) participants for anger, fear, and happiness, which are high-arousal emotions (Clark et al., 1984; Mauss and Robinson, 2009). This network was recruited early in the task. In contrast, older (but not young) participants in the P group recruited a smaller network, which emerged later (lag 4). These findings contribute to an emerging literature suggesting that OT's effects are temporally dependent (Piva and Chang, 2018) and that OT administration may shift attention early to facilitate the detection of socially salient stimuli (Domes et al., 2013; Shamay-Tsoory and Abu-Akel, 2016; but see Guastella et al., 2009).

This more widespread network recruited by older participants in the OT group included the mPFC and subgenual cingulate gyrus, regions implicated in emotional conflict regulation and appraisal (Etkin et al., 2011). In contrast, older participants in the P group recruited more parietal regions and the putamen. This pattern of findings suggests that OT may facilitate amygdalar communication with more anterior regions as a function of early orienting of attentional resources to socially relevant stimuli (Huffmeijer et al., 2013; Sander et al., 2003). OT's effects may be particularly sensitive among older adults in specific emotional contexts. Intranasal OT in this respect may be beneficial for older adults' processing of high-arousal emotions, given age-related declines in the experience of high-arousal emotions (Charles and Carstensen, 2010) and the impact of arousal on memory for high-priority information in aging (Mather and Sutherland, 2011). These hypotheses can be tested in the future by using experimental tasks that systematically incorporate emotion displays of varying valence (positive vs. negative) and arousal (low vs. high) levels.

Examination of functional connectivity can enhance our understanding of factors that impact brain processes, including age, health status, and sensitivity to pharmacological manipulation (Borsook et al., 2011; Sala-Llonch et al., 2015). Functional changes relating to healthy and pathological brain aging, in particular, have not been clearly distinguished yet in the context of social cognition (Natelson Love et al., 2015). To our knowledge, our study is the first to investigate the effects of OT on functional connectivity related to the processing of different facial emotions in healthy older adults. More research on healthy older populations is needed to follow up these findings toward uncovering functional changes relating to social cognition that stem from age-related neuropathology (Huffmeijer et al., 2013), such as in frontotemporal dementia (Jesso et al., 2011). Although a single dose of 24 IU is widely used for investigations on intranasal OT's effects on social cognition (Quintana et al., 2018), we propose that in clinical extensions of this work, use of randomized, placebo-controlled, multidose and repeated administration paradigms will be beneficial toward determination of OT's therapeutic efficacy by systematically comparing OT's effects across different dosages and across multiple administrations (Macdonald and Feifel, 2013).

7. Conclusion

In conclusion, our study provides evidence for distinct age- and OT-related, emotion-specific brain patterns and amygdalar connectivity during dynamic facial emotion identification and represents a crucial first step in a broader research program that probes the efficacy of intranasal OT on the brain and behavior in aging. Intranasal OT effects on brain pattern recruitment varied between young and older adults and by emotion. Furthermore, OT administration in older adults resulted in an amygdalar network shift for the processing of high-arousal emotions (anger, fear, happiness). Alteration of brain patterns and connectivity by age and emotion due to OT supports a discrete approach to emotion processing in adulthood and aging (Kunzmann et al., 2017). Together, these findings suggest that intranasal OT effects on the brain in healthy aging may be temporally and contextually dependent. Moving forward, fine-grained investigations on OT's temporal effects may be particularly informative for advancing our understanding of the role of OT in aging and emotion processing.

Disclosure

The authors have no actual or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2019.01.016.

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