# AGE DIFFERENTIAL EFFECTS OF OXYTOCIN ON RESTING STATE FUNCTIONAL CONNECTIVITY IN WOMEN

By

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To my husband Daniel, my best friend Jason, my mother, and my grandparents

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| | |
|---|---|
| 3D | three dimensional |
| 3T | three tesla |
| 4D | four dimensional |
| AC | anterior cingulate |
| AC-PC | anterior cingulate to posterior cingulate |
| ACC | anterior cingulate cortex |
| aIN | anterior insula |
| AMY | Amygdala |
| BOLD | blood-oxygen level dependent |
| CONN | Functional Connectivity Toolbox |
| fMRI | functional magnetic resonance imaging |
| FOV | field of view |
| IFG | inferior frontal gyrus |
| IN | Insula |
| IU | international unit |
| LOC | lateral occipital complex |
| MCC | medial cingulate cortex |
| MFG | medial frontal gyrus |
| MNI | Montreal Neurological Institute |
| MNS | mirror neuron system |
| mPFC | medial prefrontal cortex |
| MP-RAGE | magnetization-prepared rapid gradient-echo |
| MRI | magnetic resonance imaging |
| MTG | medial temporal gyrus |

| | |
|---|---|
| NAcc | nucleus accumbens |
| NITRC | Neuroimaging Informatics Tools and Resources Clearinghouse |
| OT | oxytocin |
| OXTR | oxytocin receptor |
| P | placebo |
| p-FDR | false discovery rate adjusted p-value |
| p-unc | uncorrected p value |
| PCC | posterior cingulate cortex |
| PFC | prefrontal cortex |
| PI | principle investigator |
| PNV | paraventricular nuclei |
| RMET | reading the mind in the eye task |
| ROI | region of interest |
| SON | supraoptic nuclei |
| TE | echo time |
| TI | inversion time |
| TP | temporal pole |
| TR | repetition time |
| vmPFC | ventral medial prefrontal cortex |

Abstract of Thesis Presented to the Graduate School
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Socioemotional Selectivity Theory proposes that older adults experience a shift in goals and motivation, rendering social relationships a priority. At the same time, aging is associated with change in social functioning, such as a decline in the ability to interpret the thoughts and feelings of others. These functional changes can create difficulty in the social interactions of older adults during a time in adult development when social relationships are becoming increasingly important. The neuropeptide oxytocin (OT) is associated with benefits in social functioning (e.g., enhanced ability to accurately read and interpret emotional facial expressions in others). There is growing evidence suggesting that OT acts in brain areas involved in social functioning such as the cingulate cortices, medial prefrontal cortex (mPFC), insula (IN), amygdala (AMY), and nucleus accumbens (NAcc), and that OT enhances functional connectivity among these regions and with the brain stem. However, currently, a clear understanding of the brain mechanisms underlying OT's role in social functioning is lacking. Further, the current literature, though still small, suggests that the intranasal effects of OT may vary by sex and age.

To further contribute to this currently sparse literature, this project used magnetic resonance imaging (MRI) to investigate the neural mechanisms of acute (i.e., single-dose) intranasal OT administration on resting-state functional connectivity among areas of the social brain in 20 younger (*M* = 22.7 years, *SD* = 3.28) and 23 older (*M* = 70.5 years, *SD* = 4.91) women. Participants were randomly assigned, in a double-blind between-subject design, to either self-administer 24 international units (IUs) of OT or placebo (P) nasal spray before images of their brain were taken at rest. Effects of treatment x age group on resting-state functional connectivity based on blood oxygen level dependent (BOLD) signal were investigated among regions of the social brain (i.e., anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), IN, mPFC, NAcc, AMY, and brain stem). Younger compared to older women in the P group showed greater resting-state functional connectivity between social brain regions. Younger women in the OT compared to the P group showed less resting-state functional connectivity between the brain stem and social brain regions, while there were no significant treatment-related effects within these regions for older women. These findings suggest that the effect of OT on social brain mechanisms may change over the course of the adult lifespan for women.

# CHAPTER 1
# PREVIOUS FINDINGS AND PURPOSE OF STUDY

## Age-Related Changes in Social Functioning

As individuals age, they experience a shift in priority from knowledge acquisition to a focus on social relationships (Carstensen, 2006). Accompanying this change in priority are somewhat paradoxical alterations in socioemotional information processing abilities. Some of these age-related changes appear to benefit social functioning. For instance, the ability to regulate emotions and emotional problem-solving skills tend to improve with age (Blanchard-Fields, 2007), and older are better able to ignore interference on emotional tasks compared to younger adults (Ebner & Johnson, 2010; Samanez-Larkin et al., 2009). Other social capacities, however, decline with age, such as the ability to identify emotions in others (Ebner & Johnson, 2009; Ruffman et al., 2008). Additionally, older adults show a stronger positivity bias, defined as the tendency to pay greater attention to positive stimuli relative to negative, in attention and memory in comparison to younger adults (Mather & Carstensen, 2005). For example, older adults perceive negative images to be less arousing and positive images to be more arousing than do younger adults (Moriguchi et al., 2011). Older adults also have greater difficulty identifying negative facial emotions, such as sadness or contempt, as compared to positive facial emotions (MacPherson, Phillips, & Della Sala, 2002; Ruffman et al., 2008).

The changes in processing of socioemotional information that accompany aging come during a time in the adult lifespan when the importance of social relationships is typically high (Carstensen, 2006) and may result in difficulties in social interactions for older adults. These age-related changes in socioemotional functioning are potentially

affected by multiple mechanisms working together. The underlying mechanisms, however, have currently not yet been fully explored (Ebner & Fischer, 2014). Possible processes that the literature only recently has endorsed include age-related alterations in functional activity and connectivity (FC) between regions of the “social brain” and differences in neurotransmitter level and function, such as pertaining to the neuropeptide oxytocin (OT), which has been shown to be crucially involved in socioemotional functioning and information processing.

## The “Social Brain”

Functional connectivity, measured using blood-oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI), increases in certain areas of the brain during tasks of a socioemotional nature (e.g., processing of emotional faces or biological motion). These areas, in particular the anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), medial prefrontal cortex (mPFC), the amygdala (AMY), the insula (IN), and the nucleus accumbens (NAcc), collectively form the "social brain" in humans (Adolphs, 2009).

A number of these areas serve multiple functions with regards to socioemotional processing. For example, the viewing of emotional faces is associated with increased activity in a variety of social brain areas, including the AMY, cingulate gyrus (i.e., ACC, MCC and PCC), and IN (Fusar-Poli et al., 2009; Jehna et al., 2011). The right IN and AMY are more strongly activated during imitation of positive emotional expressions than non-emotional faces (Pohl et al., 2013). Additionally, there is a greater increase in BOLD signal in the right anterior (a)IN in response to the viewing of emotional expressions (i.e., disgust and happiness), compared to neutral faces (Chen et al., 2009)

and there is evidence of bilateral aIN during responses of affective empathy (Fan et al., 2011).

Another region of the social brain, the mPFC, is strongly associated with Theory of Mind (ToM), self-directed emotional reflection, and inference of the emotional states of others (Reniers et al., 2012). There are multiple clusters in the PFC that are involved with different, though related, mentalizing tasks (Seitz, Nickel & Azari, 2006). There also appears to be an increase in activation of the mPFC during focus on internal states (Seitz, Nickel, & Azari, 2006), particularly in the ventral (v)mPFC, which shows increased activation during mentalizing tasks involving the attribution of states when the observed is similar to the observer (Mitchell, Banaji, & MacRae, 2005).

Further, during cognitive evaluation of the emotional state of others, the dorsal anterior (da)MCC is recruited (Fan et al., 2011). Reading the Mind in the Eyes task (RMET), used to detect potential deficits in ToM (Baron-Cohen et al., 2001), engages the mPFC, lateral PFC, AMY, and IN, in addition to associative areas (Pincus et al., 2010). In addition, the ACC has been shown to be involved in the ability to detect and pay attention to emotional stimuli (Lane et al., 1998).

## Resting-State Functional Connectivity and the Social Brain

Many of these social brain regions that are involved in the processing of socioemotional information during tasks are also functionally connected during rest. In fact, the literature demonstrates that this resting-state functional connectivity is associated with socioemotional functioning. For instance, resting-state functional connectivity between the right ventral aIN and bilateral brain stem is associated with empathetic phenotype (Cox et al., 2012). Resting-state functional connectivity within the default mode network (DMN), which includes the mPFC and PCC, appears to be

predictive of an individual's ability to identify with the pain of another (Otti et al., 2010). ToM reasoning is also associated with mPFC connectivity with other regions of the DMN (Spreng & Grady, 2009). These findings suggest that resting-state functional connectivity is a potentially good indicator of how well socioemotional information is being processed within and between regions of the social brain.

In summary, there is solid evidence that certain brain regions are especially involved in processing socioemotional information. These social and affective brain regions consist of the mPFC, ACC, AMY, IN, NAcc, and PCC. Functional connectivity between these regions varies by socioemotional task. Additionally, resting-state functional connectivity is indicative of socioemotional processing, making the study of it a valuable tool in understanding the brain mechanisms underlying socioemotional functioning.

## Oxytocin

OT is a nine-amino acid neuropeptide that is associated with processing of socioemotional information and functioning in social and affective domains. It is released both in the central nervous system (CNS) and peripherally (Gimpl and Fahrenholz, 2001) after being synthesized in the hypothalamic paraventrivular nuclei (PVN) and supraoptic nuclei (SON) (Insel, 2010). Within the brain, OT is released diffusely by dendrites of magnocellular neurons and neurons that project to specific regions of the limbic system, such as the AMY, hippocampus, and striatum (Landgraf and Neumann, 2004; Knobloch et al., 2012). OT appears to have a modulating effect on various socioemotional processes and social behaviors (De Dreu, 2014). However, the mechanism by which OT and other neuropeptides (e.g., arginine, vasopressin) exert their effects is complex and still poorly understood (Bethlehem et al., 2012).

## Effects of Intranasal Oxytocin on Socioemotional Functioning

There is growing evidence that intranasal administration of exogenous OT has an effect on socioemotional functioning and information processing. Intranasal administration of OT is assumed to enhance OT concentrations in the CNS and peripherally, as the intranasal application allows OT to bypass the blood-brain barrier and enter the cerebral spinal fluid (Born et al., 2002). Intranasal OT administration trials have advanced understanding of the effects of OT on social behavior in humans, however, with somewhat mixed findings.

For example, there is evidence that OT improves socially reinforced learning and emotional empathy (Hurlemann et al., 2010). Acute intranasal OT administration, compared to placebo (P), also increases performance on the RMET task, demonstrating improved ability to interpret the mental states of others (Domes et al., 2007) and increased response speed (Pincus et al., 2010). Furthermore, individuals administered intranasal OT do not decrease trust behavior after betrayal, unlike their control counterparts (Baumgartner et al., 2008). In addition to this, men administered OT intranasally show enhanced startle effects and biased memory for negative over neutral stimuli (Striepens et al., 2012) and women administered OT show an enhanced response to infants crying (Riem, et a.l, 2011), compared to those administered P.

These findings carry potential implications for clinical populations (Bartz et al., 2011; Meyer-Lindenberg et al., 2011), with possible benefits to populations that experience impaired ability to interpret the emotional states of others (Feifel et al., 2010; Guastella et al., 2009). Taken together, intranasally administered OT has offered insights into OT's role and function on socioemotional functioning. Through its intranasal application it offers an effective method to study the brain mechanisms by which the

neuropeptide exerts its effect on socioemotional functioning. However, the current literature on this topic, especially in the context of using neuroimaging tools to study OT's impact on the brain, is still sparse.

**Oxytocin Modulates Functional Connectivity between Social Brain Regions**

As shown by its effects on socioemotional functioning, the strongest targets of OT in the CNS appear to be areas of the social brain (Bethlehem et al., 2012), such as the ACC, IN, and vmPFC (Kanat, Heinrichs & Domes, 2014). However, results from neuroimaging studies investigating the effects of intranasal OT are somewhat mixed with regards to how BOLD signal and functional connectivity in these areas are affected. Further, few studies have examined the specific mechanisms of intranasal OT administration in the brain, such as with respect to its effect on resting-state functional connectivity signal in social brain regions (but see Ebner et al., 2016).

Intranasal OT compared to P administration reduces coupling between the AMY and the brainstem during emotional face processing (Kirsch, 2005). Similar reduced task-related functional coupling after OT vs. P administration is also seen between the AMY and other regions of the midbrain and the dorsal striatum (Baumgartner et al., 2008). Further, while OT decreases overall AMY activity, there is evidence of increased coupling between the AMY, IN, and inferior frontal gyrus (IFG), in response to negative stimuli in younger adult males (Striepens et al., 2012). Using a resting state paradigm, data from our own lab has shown that intranasal OT administration increases resting-state functional connectivity between the mPFC and the AMY during resting-state in younger women and older men (Ebner et al., 2016).

Taken together, the majority of neuroimaging research investigating the effects of intranasal OT administration has been focused on the AMY and previous studies are

primarily task-based. Additionally, variations of brain mechanisms underlying OT's effects across adulthood and sex differences have been largely ignored. This lack in age- and sex-comparative studies on OT's level and function in the brain is especially problematic in light of growing evidence that the effects are context and population dependent (Bakermans-Kranenburg & Ijzendoorn, 2013; Bartz et al., 2011). Furthermore, there is evidence of age- and sex-differential effects of intranasal OT administration on resting-state functional connectivity within the social brain (Ebner et al., 2016).

### Age-Related Social Brain Functional Connectivity and the Role of Oxytocin

Changes in socioemotional functioning in aging are associated with age-related changes in BOLD signal in and among areas of the social brain. In particular, several of the social brain areas show age-related changes during both task-related and resting-state fMRI. For instance, task-related differences in brain activity in single regions and functional connectivity among regions between younger and older adults have been shown for the cingulate cortices (ACC, PCC) (Chen et al., 2013), mPFC, the AMY (Moriguchi et al., 2011), the IN (Chen et al., 2013), and the NAcc (Vink et al., 2015; Rademacher et al., 2013). The literature also suggests less rsBOLD activity in general in older compared to younger adults (Damoiseaux et al., 2008), particularly in the DMN (Koch et al., 2010).

For example, older compared to younger adults showed greater activation of the NAcc in response to social but not monetary reward (Rademacher et al., 2013). Less BOLD response was seen in the anterior aIN and anterior (a)MCC of older adults while viewing pain in others compared to younger adults (Chen et al., 2013). Younger adults also demonstrated more AMY activity in emotion identification tasks than older adults

(Gunning-Dixon et al., 2003). During face processing tasks, high-performing older adults recruited additional areas not recruited by younger adults and recruited to a lesser extent by low-performing older adults (Lee et al., 2011). Thus, recruitment of alternative regions of the brain may be compensatory in older adults (Grady, 2012).

While it is known that there are changes in resting-state functional connectivity with age, most of the research has been focused on resting-state functional connectivity associations with cognitive and executive age-related change. For instance, age-related reduced resting-state functional connectivity in some areas of the brain have been correlated with reduced cognitive functioning (Damoiseaux et al., 2008). However, this line of research can still be used to inform investigations into socioemotional processing as changes in cognitive and executive functioning often occur in conjunction with changes in socioemotional domains (Charlton et al., 2009).

Currently, still little is known about the role of OT in human development in the social brain and particularly its effects in aging (but see Campbell et al., 2014; Ebner et al., 2016). Human studies on the role of OT in the aging brain refer mostly to postmortem evaluations and produced mixed findings regarding change in level and function (for reviews see Ebner et al., 2013; Huffmeijer, van IJzendoorn, & Bakermans-Kranenburg, 2012).

For instance, immunochemically identified OT neurons in the PVN and SON did not show any significant age-related decrease in postmortem investigation (Fliers et al., 1985). This stability has been demonstrated for both men and women, even in instances of Alzheimer's disease where there appears to be decreased OT secretion

(Wierda et al., 1991). However, immunoreactive OT neurons were more weakly stained in older compared to younger adults (Calza et al., 1997).

A 10-day trial of intranasal OT administration found an increase in self-reported feelings of gratitude and decreased fatigue among older men that remained at the 30-day follow-up (Barraza et al., 2013). In the only existing human fMRI study with older adults, acute intranasal OT administration altered resting-state functional connectivity between AMY and mPFC in younger women and older men but not in older women or younger men (Ebner et al., 2016).

In sum, the literature suggests that age-related changes in task-related functional connectivity are associated with changes in socioemotional functioning. Research into resting-state functional connectivity in older adults has primarily focused on associations with cognitive and executive functioning. The few studies conducted on OT's effect in human aging suggest age effects in OT function in the social brain.

**Sex Differences in Social Brain Functional Connectivity and Oxytocin**

What little investigation has been conducted on OT and human aging has occurred predominantly in men, with older women being ignored (but see Campbell et al., 2014 Ebner et al., 2015, 2016). There is evidence of sex differences in socioemotional processing and associated functional connectivity between regions of the social brain. Further, it is possible that the way men and women process socioemotional information change over the adult lifespan. Behaviorally, women typically perform better than men at emotion identification tasks, when viewing faces (Williams et al., 2009). Additionally, there are differences in resting-state functional connectivity between men and women.

For example, with regards to task-related FC, there is evidence that women recruit additional brain areas during the viewing of happy (e.g., left thalamic region) and sad (e.g., left parietal and lentiform areas) faces when compared with men, while men recruited regions that were not used by women during the processing of sad faces (e.g., right temporal and lentiform regions) (Lee et al., 2002). Additionally, women demonstrated greater bilateral AMY activation during empathic tasks, an effect which was more pronounced during the follicular phase of the menstrual cycle (Derntl et al., 2010), suggesting variations by gonadal hormone concentrations in social brain activity. Women, overall, show more bilaterally distributed activation during the viewing of positive emotional faces in comparison to men (Bourne, 2005).

Additionally, there are differences in baseline resting-state functional connectivity between men and women. For instance, biological sex is associated with resting-state functional connectivity network topological organization (Tian et al., 2011). Women show greater resting-state functional connectivity in cerebellar, frontal, and temporal regions of the brain than men (Filippi et al., 2012). Women also demonstrate greater resting-state functional connectivity in the PFC than men, with the effect being stable throughout the menstrual cycle (Hjelmervik et al., 2014).

Overall, the literature agrees on the existence of differences in the way men and women process socioemotional information in the brain. However, the literature is quite mixed as to the specifics of these differences. This is confounded by the variations in functional connectivity between regions of the social brain in women during the different stages of the menstrual cycle, suggesting the importance of gonadal hormones on functional connectivity in the social brain.

Studies investigating neural response to intranasal OT in women are limited with much of our knowledge on sex differences coming from animal models. The few studies comparing women and men suggest that OT may act sex-differentially. For example, acute intranasal OT administration results in opposing effects on the functional connectivity in men and women, with social brain activity of men in the OT group being more similar to that of women in the P group and vice versa (Rilling, 2014). Also, unlike in men, women showed greater AMY activation in response to threatening stimuli following acute OT administration compared to P (Lischke et al., 2012).

Studies looking at sex-dependent effects of OT on older adults are distinctly lacking from the literature (but see Ebner et al., 2016) despite the evidence that OT has sex-differential effects on social brain regions in younger adults. In the single study to investigate both sex and age-differential effects of OT on rsFC, OT increased connectivity between AMY and mPFC in younger but not older women and older but not younger men (Ebner et al., 2016).

## Purpose of Current Study

The current study provides novel contributions to the fields of developmental psychology and neuroscience. Age-related changes in socioemotional functioning are likely related to age-related changes in functional connectivity and neurotransmitter (e.g., OT) level and function in regions of the social brain. However, currently, very few studies have explicitly investigated the role of OT in the aging social brain. Further, even though there is growing evidence of sex-dependent variation in OT's effect on the social brain, currently intranasal OT administration studies with women are sparse, particularly older women. Additionally, neuroimaging research on the effects of intranasal OT administration in humans is primarily focused on AMY, with little investigation into other

regions of the social brain. The present study specifically addressed these research gaps by (i) examining the differences in resting-state functional connectivity within social brain regions among younger and older women and (ii) determining effects of intranasal OT administration on resting-state functional connectivity among regions of the social brain in these younger and older women.

## Specific Aims and Hypotheses

Going beyond previous work, this project examined differences in resting-state functional connectivity within social brain regions among younger and older women (Aim 1) and determined effects of intranasal OT administration on resting-state functional connectivity among social brain region in younger and older women (Aim 2). The social brain regions of interest (ROIs) were the ACC, PCC, AMY, IN, mPFC, brain stem, and NAcc.

**Aim 1.** To determine differences in resting-state functional connectivity among areas of the social brain between young and older women. Older compared to younger women will show less resting-state functional connectivity among social brain regions (Hypothesis 1).

**Aim 2.** To determine age-differential effects of intranasal OT administration on resting-state functional connectivity among areas of the social brain in women. There will be greater resting-state functional connectivity between social brain ROIs for the OT compared to the P condition in women (Hypothesis 2a). Additionally, this effect will vary between be younger and older women with older women showing a greater increase in resting-state functional connectivity between social brain ROIs in the OT compared to P condition than younger women (Hypothesis 2b).

# CHAPTER 2
# METHODS

## Participants

rsBOLD data was collected from 83 of the 102 volunteers from a larger project conducted in the Department of Psychology, at the Institute on Aging, and at the McKnight Brain Institute at University of Florida between August 2013 and October 2014. One participant was excluded due to scan image corruption, and three more participants due to excessive head motion. Scan data from a total of 79 participants was processed. The rsBOLD data from the 43 women who participated was submitted to analysis: 20 younger (*M* = 22.7 years, *SD* = 3.28) and 23 older (*M* = 70.5 years, *SD* = 4.91) white, English-speaking adult women. Older participants scored $\geq$ 30 on the Telephone Interview for Cognitive Status (Brandt et al., 1988). All women in the older group were postmenopausal and all women in the younger group were premenopausal, with ten of the younger women in the follicular phase of their menstrual cycle and seven of the younger women on oral contraception when nasal spray administration took place.

Participant recruitment occurred through mailouts and fliers distributed throughout the community and campus. Self-report physical and cognitive health screenings took place by phone and during an on-campus visit. Those who were pregnant, breastfeeding, had a psychological disorder, severe or progressive medical illness, known allergies to the preservatives in the nasal spray, any contraindication to MRI, and excessive smoking or drinking were excluded from the study.

Of the 43 participants with rsBOLD data, 11 younger and 10 older women were randomly assigned to self-administer 24 IUs of OT via nasal spray with one puff per

nostril (see procedures below for details). Nine younger and 13 older women self-administered a P, containing all other ingredients but the OT.

## Procedure

The study comprised two sessions consisting of a screening visit and a full study visit in the context of a larger project. All study sessions were conducted by trained project staff. Instructions were given to participants to stay well-hydrated and abstain from smoking, caffeine, alcohol, and use of recreational drugs in the 24 hours, and from food, exercise, or engagement in sexual activity in the two hours, leading up to their appointment. All test sessions occurred in the mornings, with 8 AM being the typical start time. Written informed consent was obtained following a description of the study.

During the screening visit, participants completed the Digit Symbol Substitution (DSS) task to measure sensorimotor speed (Wechsler, 1981) and the Rey Verbal Learning Memory (RVLM) task (Rey, 1964) as a measure of short-term verbal memory during screening. Participants also responded to the Experiences in Close Relationship Scale (ECR)-Short Form (Wei, Russell, Mallinckrodt, & Vogel, 2007) and the Ten-Item Personality Inventory (TIPI; Gosling, Rentfrow, & Swann, 2003). Additionally, participants underwent a blood test and a health review, which covered major bodily systems.

At the start of the full study visit, participants rated their current mood via the brief Positive Affect Negative Affect Scale (PANAS; Watson, Clark, & Tellegen, 1988) immediately prior to the nasal spray application. Nasal spray administration followed recommendations for the standardized administration of intranasal OT (Guastella et al., 2013). Randomization was double-blind and overseen by the study PI.

The 8-minute, open-eye rsBOLD scan occurred between 70-90 minutes after the administration of the OT spray and followed structural and task-related BOLD scans. Participants lay supine on the MRI scanner bed with their heads comfortably positioned. Cushions surrounding the head were used to stabilize and reduce motion. Instructions were given over the intercom for participants to relax and to look at a white fixation cross on a gray screen. After the scan, participants completed various self-report measures outside the scanner in the context of the larger research project. Participants were debriefed at the completion of the study visit. All procedures were in accordance with the study protocol, which was approved by the Institutional Review Board at University of Florida. There were no adverse side effects reported.

**Image Acquisition**

All brain images, both structural and BOLD, were acquired at the McKnight Brain Institute at the University of Florida using a 3 Tesla (3T) Philips Achieva MR Scanner (Philips Medical Systems, Best, The Netherlands) with a 32-channel head coil. A high resolution, whole-brain, structural T1-weighted (T1) scan using a three-dimensional (3D) magnetization-prepared rapid gradient-echo (MP-RAGE) sequence (sagittal plane, TR/TE/TI = 7/3.2/2750 ms, flip angle = 8°; in-plane FOV = 240 mm x 240 mm; imaging matrix 240 x 240; 170 contiguous sagittal slices with 1 mm slice thickness, 1x1x1$mm^3$ isotropic voxels) and a tilted acquisition in an oblique orientation at 30° to the AC-PC line, single-shot gradient echo, echo-planar imaging sequence sensitized to blood oxygenation level dependent (BOLD) contrast (TR = 2000 ms, TE = 30 ms, flip angle = 90°, in-plane FOV = 240 mm x 240 mm, 80x80 matrix size, 3x3x3$mm^3$ isotropic voxels, 38 interleaved axial slices, zero inter-slice gap) were acquired using for each participant.

## Image Preprocessing

Preprocessing of rsBOLD and T1 MPRAGE scans using SPM12 and Functional Connectivity Toolbox (CONN; http://www.nitrc.org/projects/conn/; Whitfield-Gabrieli & Nieto-Castanon, 2012) version 17b, from the Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC) included: functional realignment and unwarping, subject motion estimation and correction, functional and structural center translation to coordinates (0,0,0), ART-based outlier scan detection and scrubbing, functional and structural segmentation and normalization to MNI, and functional smoothing with an 8mm Gaussian kernel (Whitfield-Gabrieli & Nieto-Castanon, 2012). White matter and cerebral spinal fluid noise was corrected for using “aCompCor,” anatomically informed component-based noise correction (Behzadi et al., 2007).

## Statistical Analyses

All analyses were conducted using CONN (http://www.nitrc.org/projects/conn/; Whitfield-Gabrieli & Nieto-Castanon, 2012), adopting an age group (younger vs. older) x treatment (OT vs. P) between-group factorial design. A ROI-to-ROI approach was used, with ACC, PCC, NAcc, IN, mPFC, AMY and the brain stem, defined within the CONN software. Results were corrected for multiple comparisons across all ROIs. T-tests used connection-level corrections while F-tests used network-level thresholds with the false discovery rate-corrected p-values (p-FDR) used as an analysis-wise false positive control method. Functional connectivity (measured in effect size of the BOLD signal relationships over the timecourse between ROIs) between these regions during resting state constituted the central outcome variable, resting-state functional connectivity.

**Aim 1**. Aim 1 considered only participants in the P group, as OT administration may confound age effects. To address this aim regarding age differences in resting-

state functional connectivity among areas of the social brain (Hypothesis 1), independent t-tests, for each ROI to each other ROI, contrasting younger and older women were conducted on social brain resting-state functional connectivity. Seed-level corrections were performed for each ROI to ROI analysis. The independent variable was age. The dependent variable was resting-state functional connectivity BOLD signal between ROIs of the social brain.

**Aim 2**. Aim 2 compared participants in the P group to participants in the OT group. To test Hypothesis 2a regarding main treatment effects, ROI to ROI independent t-tests contrasting P and OT conditions across younger and older women were conducted, with seed-level corrections performed for each ROI to ROI analysis. The independent variable was the treatment condition (P vs OT). The dependent variable was resting-state functional connectivity BOLD signal between ROIs of the social brain. To test Hypothesis 2b regarding treatment by age effects in resting-state functional connectivity among areas of the social brain, ROI to ROI F-test contrasts were conducted, with network-level corrections performed. The independent variables in this analysis were age and treatment condition. The dependent variable was resting-state functional connectivity BOLD signal between ROIs of the social brain.

Table 2-1. Means and standard deviations and differences between younger and older women for chronological age, education level, and cognitive function.

| Measures | Younger Participants M (SD) | Older Participants M (SD) | Age Differences |
|---|---|---|---|
| Age (in years) | 22.74 (3.28) | 70.47 (4.91) | $F(1,41) = 1360.34$, $p < 0.001$ |
| Education Level (in years) | 16.15 (3.10) | 16.52 (3.27) | $F(1,41) = 0.14$, $p = 0.705$ |
| Rey Auditory Verbal Learning Test (total correct) | 9.30 (1.42) | 8.17 (2.53) | $F(1,41) = 3.10$, $p = 0.086$ |

Notes: Education level was measured in total years of formal education (with missing data for one older participant). Short-term verbal memory was measured by total items correct in the Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1964). M = Mean; SD = Standard Deviation.

Table 2-2. Means and standard deviations and differences between younger and older women in positive and negative affect.

| Measures | Younger Participants M (SD) | Older Participants M (SD) | Age Differences |
|---|---|---|---|
| Positive Affect | 34.74 (9.06) | 41.04 (6.24) | $F(1,40) = 7.09$, $p = 0.011$ |
| Negative Affect | 15.40 (2.26) | 17.09 (4.71) | $F(1,40) = 2.13$, $p = 0.152$ |

Notes: Positive Affect Negative Affect Scale (PANAS) measured current mood at the time of the visit (Watson, Clark, & Tellegen, 1988). One younger woman from the P group was missing PANAS data for positive affect and one older woman from the P group was missing PANAS data for negative affect. M = Mean, SD = Standard deviation.

Table 2-3. Means and standard deviations and differences between women in the OT and P group for positive and negative affect.

| PANAS | OT<br>M (SD) | P<br>M (SD) | Treatment-group Differences |
|---|---|---|---|
| Positive Affect | 36.95 (7.97) | 39.43 (8.41) | $F(1,40) = 0.96$, $p = 0.333$ |
| Negative Affect | 16.57 (3.80) | 16.00 (3.27) | $F(1,40) = 0.23$, $p = 0.632$ |

Notes: Positive Affect Negative Affect Scale (PANAS) measured current mood at the time of the visit (Watson, Clark, & Tellegen, 1988). One younger woman from the P group was missing PANAS data for positive affect and one older woman from the P group was missing PANAS data for negative affect. M = Mean, SD = Standard deviation.

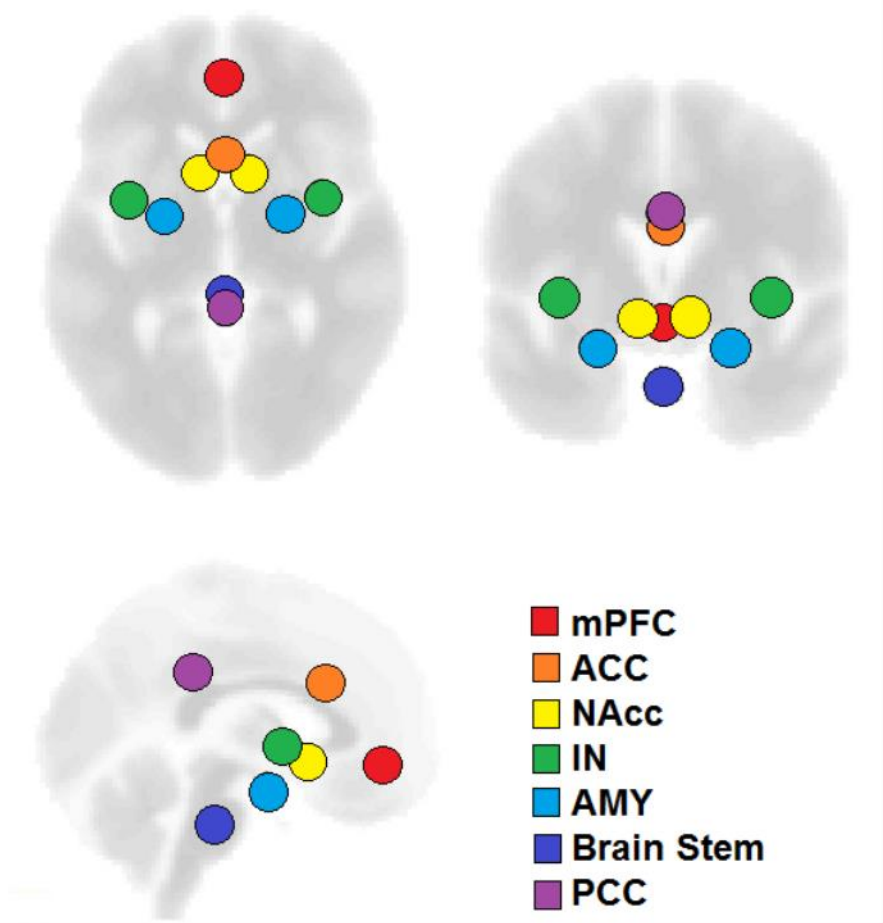


Figure 2-1. Social brain region of interest locations.

Notes: p-unc = uncorrected p-value, p-FDR = false discovery rate adjusted p-value, ACC = Anterior Cingulate Cortex, AMY = Amygdala, IN = Insula, mPFC = medial prefrontal cortex, NAcc = Nucleus Accumbens, PCC = posterior cingulate cortex.

Table 2-4. Anatomical locations (MNI space) of social brain regions used in the analyses as defined within CONN software.

| Regions | Hemisphere | MNI [X Y Z] |
|---|---|---|
| Medial Prefrontal | | [0,43,-19] |
| Anterior Cingulate | | [1,18,24] |
| Nucleus Accumbens | R | [9,12,-7] |
| | L | [-9,11,-7] |
| Insula | R | [37,3,0] |
| | L | [-36,1,0] |
| Amygdala | R | [23,-4,-18] |
| | L | [-23,-5,-18] |
| Brain Stem | | [0,-30,-35] |
| Posterior Cingulate | | [1,-37,30] |

Notes: Regions of interest are sorted in the table from anterior to posterior. Hemisphere: L = left, R = right; MNI coordinates: X = right/left, Y = anterior/posterior, Z = superior/inferior.

# CHAPTER 3
# RESULTS

## Aim 1: Age Differences in Resting-State Functional Connectivity among Areas of the Social Brain in Women

The AMY showed greater resting-state functional connectivity bilaterally with multiple other regions of the social brain for younger than older women. In particular, the left AMY showed significantly greater resting-state functional connectivity with left NAcc ($T(19) = 3.03$, $p = 0.031$), left IN ($T(19) = 2.44$, $p = 0.039$), right IN ($T(19) = 2.22$, $p = 0.043$), and right AMY ($T(19) = 2.42$, $p = 0.039$) for younger compared to older women (Figure 3-1). Similarly, the right AMY showed significantly greater resting-state functional connectivity with left AMY ($T(19) = 2.42$, $p = 0.029$), right IN ($T(19) = 2.89$, $p = 0.021$), left IN ($T(19) = 2.58$ , $p = 0.027$), and right NAcc ($T(19) = 2.88$, $p = 0.021$) for younger compared to older women (Figure 3-2). Additionally, the left IN showed greater resting-state functional connectivity with the left NAcc in younger than older women in the P group ($T(19) = 2.43$, $p = 0.038$) (Figure 3-3). This confirmed Hypothesis 1 that younger compared to older women show greater resting-state functional connectivity between social brain ROIs.

## Aim 2: Age by Treatment Interactions in Resting-State Functional Connectivity between Social Brain Regions in Women

### Main Treatment Effect across Younger and Older Women

Participants in the OT compared to the P group showed significantly less resting-state functional connectivity of the brain stem with the right IN ($T(40) = -2.91$, $p = 0.038$) and the right AMY ($T(40) = -2.77$, $p = 0.038$) (Figure 3-4). These results were contrary to Hypothesis 2a which predicted greater resting-state functional connectivity between social brain ROIs for OT compared to P.

### Age by Treatment Interactions

There was a significant treatment by age interaction for NAcc with other social brain regions bilaterally. In particular, the right NAcc showed a significant treatment by age interactions for resting-state functional connectivity with the ACC ($F(2)(39) = 5.43$, $p = 0.037$) and the left AMY ($F(2)(39) = 5.80$, $p = 0.037$) with younger women showing greater resting-state functional connectivity than older women between these regions after OT administration (Figure 3-5). Similarly, the left NAcc showed significant age by treatment interactions for resting-state functional connectivity with the ACC ($F(2)(39) = 7.19$, $p = 0.020$), left AMY ($F(2)(39) = 5.15$, $p = 0.046$), and right AMY($F(2)(39) = 4.64$, $p = 0.047$) with greater resting-state functional connectivity between these regions occurring in younger women than older women both before and after OT administration (Figure 3-6). This partially confirmed Hypothesis 2b which predicted significant age by treatment interactions in social brain resting-state functional connectivity. However, that younger women showed greater resting-state functional connectivity than older women was contrary to the direction of the effect of Hypothesis 2b.

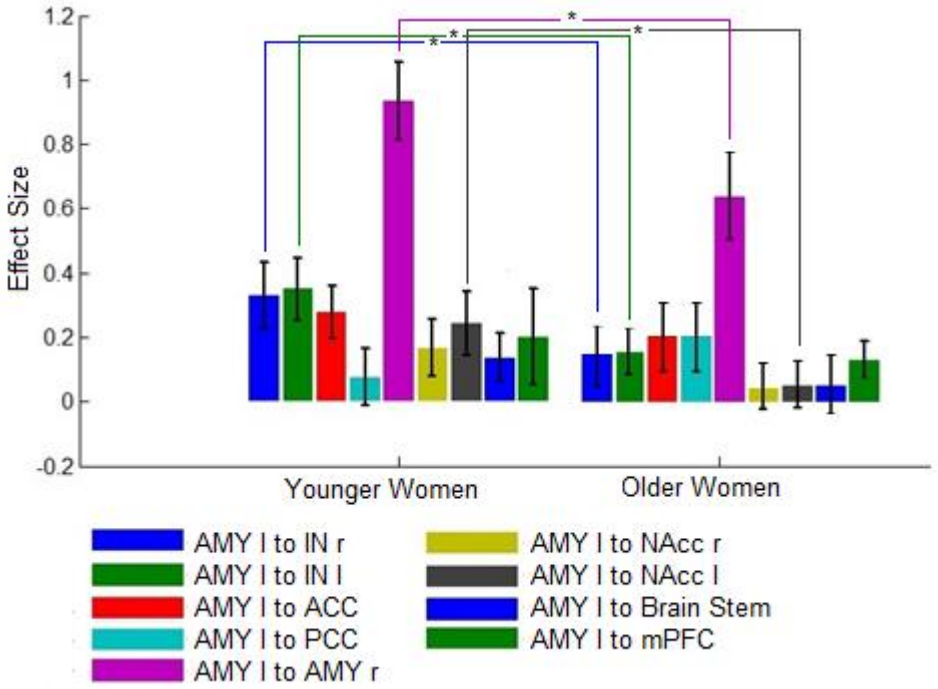


Figure 3-1. Social brain region of interest to social brain region of interest effect sizes for placebo condition with the left amygdala (AMY l) as the seed region.

Notes: Confidence intervals (CI) at 95% for effect sizes are shown. Asterisk (*) above a bar indicates a significant difference in effect size between groups. ACC = Anterior Cingulate Cortex, AMY = Amygdala, IN = Insula, mPFC = medial prefrontal cortex, NAcc = Nucleus Accumbens, PCC = posterior cingulate cortex, l = left, r = right.

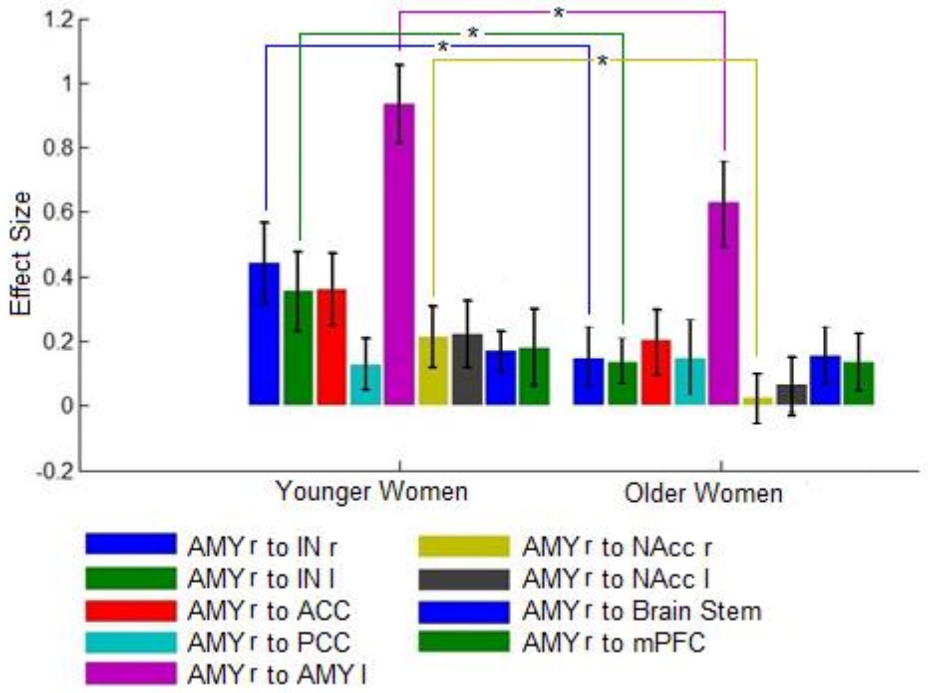


Figure 3-2. Social brain region of interest to social brain region of interest effect sizes for placebo condition with the right amygdala (AMY r) as the seed region.

Notes: Confidence intervals (CI) at 95% for effect sizes are shown. Asterisk (*) above a bar indicates a significant difference in effect size between groups. ACC = Anterior Cingulate Cortex, AMY = Amygdala, IN = Insula, mPFC = medial prefrontal cortex, NAcc = Nucleus Accumbens, PCC = posterior cingulate cortex, l = left, r = right.

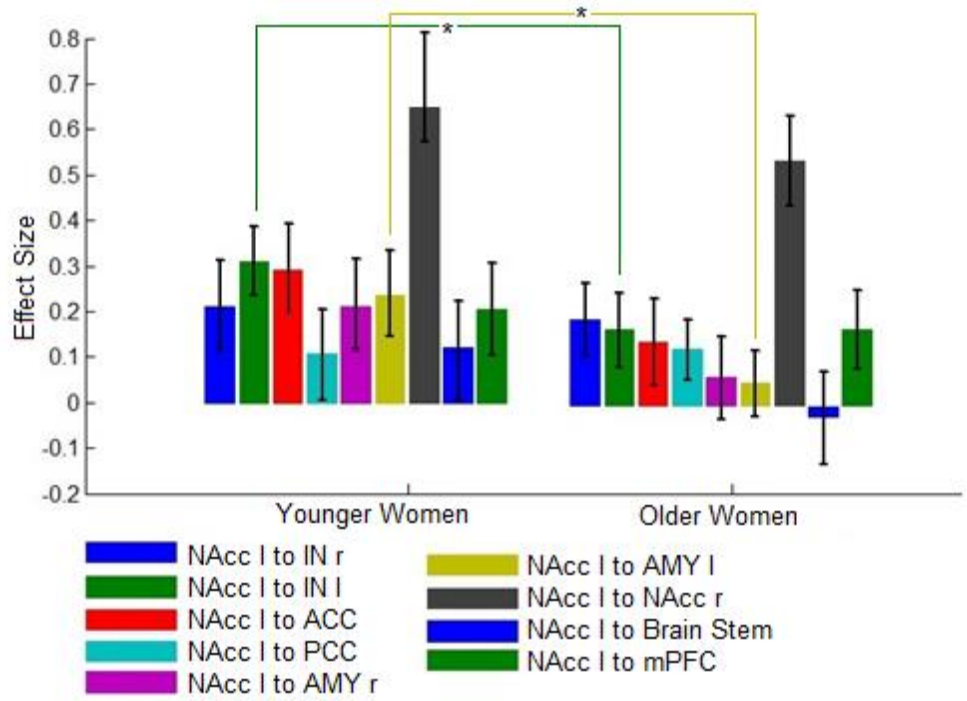


Figure 3-3. Social brain region of interest to social brain region of interest effect sizes for placebo condition with the left nucleus accumbens (NAcc l) as the seed region.

Notes: Confidence intervals (CI) at 95% for effect sizes are shown. Asterisk (*) above a bar indicates a significant difference in effect size between groups. ACC = Anterior Cingulate Cortex, AMY = Amygdala, IN = Insula, mPFC = medial prefrontal cortex, NAcc = Nucleus Accumbens, PCC = posterior cingulate cortex, l = left, r = right.

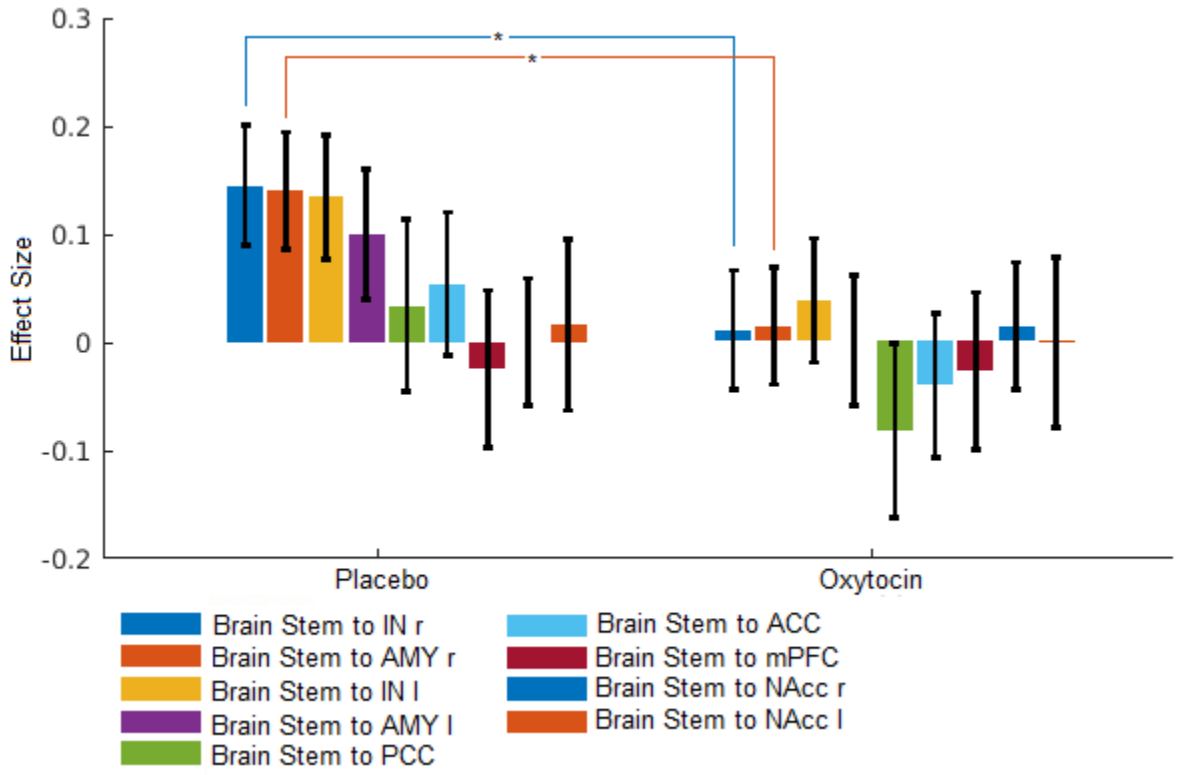


Figure 3-4. Social brain region of interest to social brain region of interest effect sizes for main treatment effects with brain stem as the seed region.

Notes: Confidence intervals (CI) at 95% for effect sizes are shown. Asterisk (*) above a bar indicates a significant difference in effect size between groups. ACC = Anterior Cingulate Cortex, AMY = Amygdala, IN = Insula, mPFC = medial prefrontal cortex, NAcc = Nucleus Accumbens, PCC = posterior cingulate cortex, l = left, r = right.

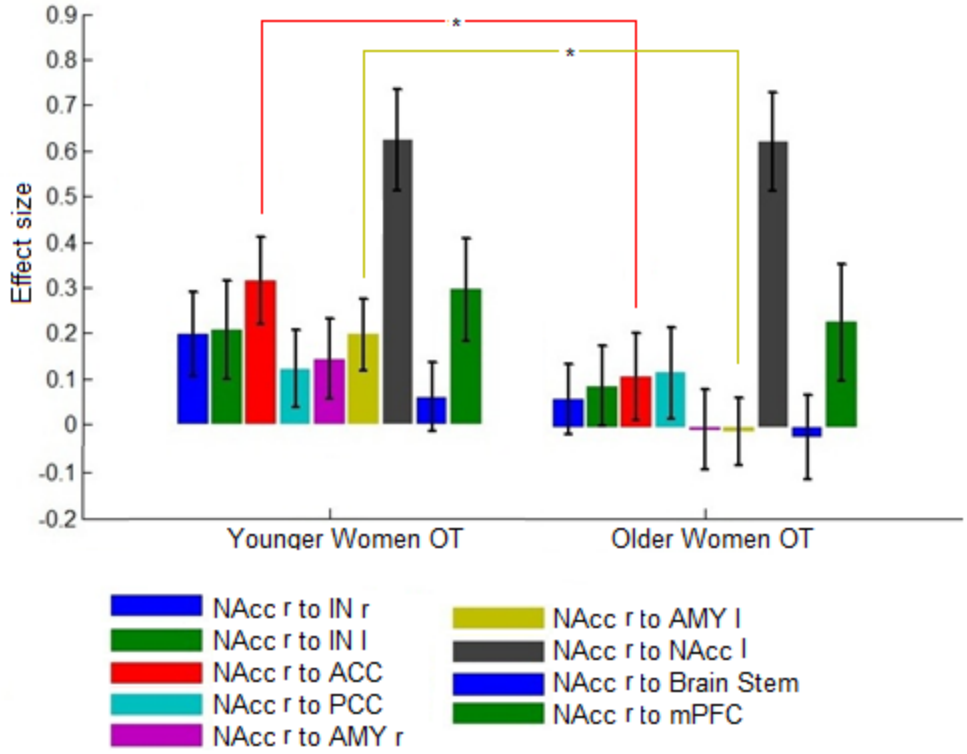


Figure 3-5. Social brain region of interest to social brain region of interest effect sizes for age by treatment effects with the right nucleus accumbens (NAcc r) as the seed region.

Notes: Confidence intervals (CI) at 95% for effect sizes are shown. Asterisk (*) above a bar indicates a significant interaction. ACC = Anterior Cingulate Cortex, AMY = Amygdala, IN = Insula, mPFC = medial prefrontal cortex, NAcc = Nucleus Accumbens, PCC = posterior cingulate cortex, l = left, r = right.

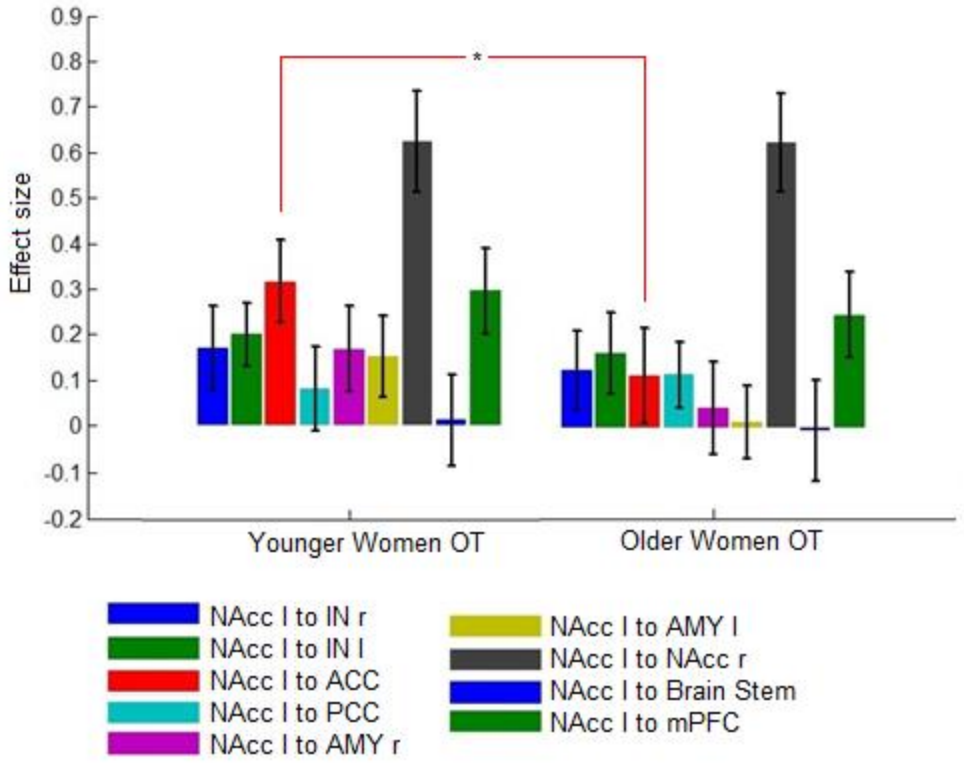


Figure 3-6. Social brain region of interest to social brain region of interest effect sizes for age by treatment effects with the left nucleus accumbens (NAcc l) as the seed region.

Notes: Confidence intervals (CI) at 95% for effect sizes are shown. Asterisk (*) above a bar indicates a significant interaction. ACC = Anterior Cingulate Cortex, AMY = Amygdala, IN = Insula, mPFC = medial prefrontal cortex, NAcc = Nucleus Accumbens, PCC = posterior cingulate cortex, l = left, r = right.

# CHAPTER 4
# DISCUSSION AND CONCLUSION

## Discussion

This project had two aims: (1) to determine resting-state functional connectivity differences between regions of the social brain in younger compared to older women; (2) to determine the age by treatment effects of intranasal OT on resting-state functional connectivity in women. The results of this were younger women showed greater resting-state functional connectivity between social brain regions than older women during placebo condition. Further, the main treatment effect of OT for women was reduced resting-state functional connectivity of the brain stem with other regions of the social brain. Additionally, there existed an age by treatment effect on the NAcc bilaterally, with greater resting-state functional connectivity between social brain regions for younger women than older women even after OT administration. These three main findings will be discussed in the following will be discussed in further detail next.

### Greater Social Brain Resting-State Functional Connectivity in Younger Compared to Older Women

Younger compared to older women in the P condition showed significantly greater resting-state functional connectivity between the bilateral AMY and bilateral IN, with involvement of the NAcc. This finding is in line with previous research demonstrating that older adults have reduced resting-state functional connectivity compared to younger adults (Damoiseaux et al., 2008; Koch et al., 2010). These differences in resting-state functional connectivity are consistent with evidence of task-related differences in social brain FC, particularly among the AMY (Moriguchi et al., 2011), IN (Chen et al., 2013), and the NAcc (Vink et al., 2015; Rademacher et al., 2013).

Samanez-Larkin and D'Esposito (2008) caution against direct comparisons of younger and older individuals in studies of healthy aging, citing group differences in hemodynamics and brain morphology. That is, resting-state functional connectivity differences between younger and older women seen in this project could simply be the result of age-related changes in brain structure or hemodynamics. However, age-related reductions in gray matter volume and white matter connectivity have been associated with decreased ToM and RMET performance (Cabinio et al., 2015). It's not just in aging that brain structure-related differences in behavioral phenotype are seen. Interindividual variability in white and gray matter structure in the brain are associated with a variety of cognitive functions and behaviors (Kanai & Rees, 2011). Future directions for this work could examine these relationships.

It is possible that hormonal differences between younger and older women underlie the observed age differences in resting-state functional connectivity. Fluctuations in ovarian hormones (e.g., estrogen and progesterone) are known to influence socioemotional processing in the brain (Toffoletto et al., 2014). All the older women in the present study were postmenopausal while the younger women were in varying stages of their menstrual cycles. Future direction should include hormone levels into consideration when comparing resting-state functional connectivity among social brain regions among women of different ages.

### Reduced Brain Stem Resting State Functional Connectivity with Regions of the Social Brain for Oxytocin Compared to Placebo Treatment

Significantly less resting-state functional connectivity was found for the brain stem with the right IN and right AMY in women for OT compared to P treatment groups. Even though not consistent with the original predictions, it is not surprising that these

areas appear to be targets for OT given that neuronal projections from which the neuropeptide is released terminate in the limbic system and striatum (Landgraf and Neumann, 2004; Knobloch et al., 2012). Also, this finding is in line with the task-based functional connectivity literature suggesting that younger men show significantly decreased functional connectivity between the brain stem and AMY during emotional face tasks after intranasal OT administration (Kirsch, 2005). Although the current project is the first study to specifically investigate resting-state functional connectivity between the IN and brain stem, other studies have demonstrated that intranasal OT administration has a modulatory effect on task-based IN activity in women (Riem et al., 2011).

### Greater Bilateral Nucleus Accumbens Resting State Functional Connectivity for Younger Women than Older Women and after Oxytocin Administration

Resting-state functional connectivity of the bilateral NAcc with other regions of the social brain varied by age and treatment. A recent study supported the involvement of OT in NAcc regulation via ventral tegmental area projections to the region, though in an animal model (Hung et al., 2017). As the endogenous OT is also released in to the striatum by neuronal projections (Landgraf & Neumann, 2004; Knobloch et al., 2012), it seems reasonable to assume that structures within the reward processing structures (e.g. striatum) would be potential targets for both endogenous and intranasally administered OT. This would include the NAcc, given its heavy involvement in social reward and its location within the striatum.

Future research should include additional brain regions besides those in the limbic system. For example, further analyses should include additional regions of the

striatum and basal ganglia involved in reward processing, such as the caudate, putamen, and pallidum.

## Limitations and Future Directions

Although the specific mechanism is not yet known, there are interactions between estrogen and OT levels and function in the CNS (Acevedo-Rodriguez, Mani, & Handa, 2015). In fact, women may be differently affected during different stages of their menstrual cycle. For example, women demonstrated greater task-related bilateral AMY activation during the follicular phase of their menstrual cycle (Derntl et al., 2010). The current project sample size was not large enough to delve in to differences in resting-state functional connectivity during different phases of the menstrual cycle in women or the effects of menstrual cycle on OT function. Additionally, all the older women who participated in this study were post-menopausal. Investigation in to the relationship between estradiol levels and the efficacy of intranasal OT would potentially be of interest for future study.

The half-life of OT is approximately 20 minutes (Bethlehem et al., 2013) while the acute effects are known to last for around 2.5 hours (Gossen et al., 2012). However, the resting-state BOLD scan took place around 70 – 90 minutes post administration of OT in the present study. This may not be close enough to the time of administration for the observation of more profound or peak effects of OT on resting-state BOLD signal in the brain.

Given that OT is a diffuse neuropeptide and that it is released by neuronal projections to limbic and striatum regions (Landgraf and Neumann, 2004; Knobloch et al., 2012), future investigations should focus on additional regions of the brain, including regions of the cortex. For instance, the frontal (IFG and medial frontal) and fusiform gyri

are also involved in socioemotional information processing and social functioning (Fusar-Poli et al., 2009; Jehna et al., 2011). Additionally, the dopaminergic neuron rich striatum regions, such as the caudate and putamen, are associated with the processing of reward stimuli including rewards of a social nature (Wake & Izuma, 2017). The projection of SON neurons to and the involvement of these structures in social functioning makes them strong potential targets for OT. Additionally, recent literature presenting evidence in favor of the hypothesis that OT affects the reward system describes the effects of intranasal OT on the NAcc functional connectivity for younger adults.

A future direction of this work would be to determine the long-term effects of intranasal OT administration. In general, there is a lack of literature investigating the long-term effects of regular intranasal OT administration in both aging populations and in women. Future directions for this research should include investigations in to age and sex-differential effects long-term effects of OT administration on healthy adults.

Additionally, there was no baseline for comparison in this study. In the future, it may be valuable to collect MRI scan data prior to administration of intranasal OT or P. A two-visit study, in which no OT or P is administered during the first visit to acquire an accurate baseline of functional connectivity and brain structure, would be beneficial to the understanding of the changes in the brain affected by acute OT administration. This would also help us gain a better understanding of how interindividual differences play a role in the effects of OT on functional connectivity in the brain.

## Conclusion

This project provides evidence of age differences in functional connectivity between regions of the brain involved in socioemotional processing in women. Women

who self-administered intranasal OT showed less resting-state functional connectivity between the brainstem and social brain regions, namely the right AMY and IN, than those in the P condition. Additionally, age by treatment interactions were found for the bilateral NAcc with the AMY and ACC. These findings provide evidence of an age variation of OT's effect on resting-state functional connectivity among social brain regions in women. This finding holds potential implications for the use of OT as an intervention for socioemotional deficits in both normal aging and clinical populations for women. Further research into the mechanisms behind these age differences is needed to better understand the potential changes in OT function and levels in healthy aging and the changes in socioemotional processing that accompany them.

# APPENDIX A
# TABLES OF SIGNIFICANT DIFFERENCES

Table A-1. Significant differences in resting-state functional connectivity between social brain regions of interest for younger compared to older women in the placebo group.

| Seed ROI | Target ROI | Statistic | p-unc | p-FDR |
|---|---|---|---|---|
| IN l | NAcc l | T(19) = 2.43 | 0.0127 | 0.0380 |
| AMY l | NAcc l | T(19) = 3.03 | 0.0034 | 0.0308 |
| | IN l | T(19) = 2.44 | 0.0123 | 0.0389 |
| | AMY r | T(19) = 2.42 | 0.0130 | 0.0389 |
| | IN r | T(19) = 2.22 | 0.0193 | 0.0435 |
| AMY r | IN r | T(19) = 2.89 | 0.0047 | 0.0214 |
| | NAcc r | T(19) = 2.88 | 0.0048 | 0.0214 |
| | IN l | T(19) = 2.58 | 0.0092 | 0.0275 |
| | AMY l | T(19) = 2.42 | 0.0130 | 0.0292 |

Notes: p-unc = uncorrected p-value, p-FDR = false discovery rate adjusted p-value, ACC = Anterior Cingulate Cortex, AMY = Amygdala, IN = Insula, mPFC = medial prefrontal cortex, NAcc = Nucleus Accumbens, PCC = posterior cingulate cortex, l = left, r = right.

Table A-2. Main effect of oxytocin treatment on resting-state functional connectivity between social brain regions for placebo compared to oxytocin.

| Seed ROI | Target ROI | Statistic | p-unc | p-FDR |
|---|---|---|---|---|
| Brain Stem | IN r | T(40) = -2.91 | 0.0058 | 0.0383 |
| | AMY r | T(40) = -2.77 | 0.0085 | 0.0383 |

Table A-3. Significant age by treatment interactions in resting-state functional connectivity between social brain regions.

| Seed ROI | Target ROI | Statistic | p-unc | p-FDR |
|---|---|---|---|---|
| NAcc l | ACC | F(2)(39) = 5.43 | 0.0083 | 0.0374 |
| | AMY l | F(2)(39) = 5.80 | 0.0062 | 0.0374 |
| NAcc r | ACC | F(2)(39) = 7.19 | 0.0022 | 0.0198 |
| | AMY l | F(2)(39) = 5.15 | 0.0103 | 0.0464 |
| | AMY r | F(2)(39) = 4.64 | 0.0156 | 0.0468 |

APPENDIX B
TABLES OF NETWORK DIFFERENCES

Table B-1. Network differences in resting-state functional connectivity for seed regions of interest with other social brain regions for younger compared to older women during placebo condition.

| Seed ROI | Statistic | p-unc | p-FDR |
|---|---|---|---|
| ACC | F(5)(15) = 1.66<br>Intensity=0.00<br>Size=0 | 0.2056 | 0.3203 |
| AMY l | F(5)(15) = 4.05<br>Intensity=10.11<br>Size=4 | 0.0158 | 0.0966 |
| AMY r | F(5)(15) = 3.84<br>Intensity = 10.76<br>Size = 4 | 0.0193 | 0.0966 |
| Brain Stem | F(5)(15) = 0.83<br>Intensity = 0.00<br>Size = 0 | 0.5493 | 0.5493 |
| IN l | F(5)(15) = 1.58<br>Intensity = 7.45<br>Size = 3 | 0.2242 | 0.3203 |
| IN r | F(5)(15) = 2.05<br>Intensity = 2.89<br>Size = 1 | 0.1297 | 0.2603 |
| mPFC | F(5)(16) = 1.18<br>Intensity=0.00<br>Size=0 | 0.3656 | 0.4570 |
| NAcc l | F(5)(15) = 2.45<br>Intensity = 3.03<br>Size = 1 | 0.0822 | 0.2603 |
| NAcc r | F(5)(15) = 2.04<br>Intensity=2.88<br>Size=1 | 0.1301 | 0.2603 |
| PCC | F(5)(16) = 0.93<br>Intensity=0.00<br>Size=0 | 0.4892 | 0.5435 |

Notes: p-unc = uncorrected p-value, p-FDR = false discovery rate adjusted p-value, ACC = Anterior Cingulate Cortex, AMY = Amygdala, IN = Insula, mPFC = medial prefrontal cortex, NAcc = Nucleus Accumbens, PCC = posterior cingulate cortex, l = left, r = right.

Table B-2. Main treatment effect network differences in resting-state functional connectivity for seed regions of interest with other social brain regions for placebo compared to oxytocin.

| Seed ROI | Statistic | p-unc | p-FDR |
|---|---|---|---|
| IN r | F(9)(32) = 1.74<br>Intensity = 0.00<br>Size = 0 | 0.1195 | 0.7957 |
| Brain Stem | F(9)(32) = 1.45<br>Intensity = 5.68<br>Size = 2 | 0.2102 | 0.7957 |
| ACC | F(9)(32) = 1.09<br>Intensity = 0.00<br>Size = 0 | 0.3959 | 0.7957 |
| IN l | F(9)(32) = 1.05<br>Intensity = 0.00<br>Size = 0 | 0.4223 | 0.7957 |
| PCC | F(9)(32) = 1.02<br>Intensity = 0.00<br>Size = 0 | 0.4484 | 0.7957 |
| NAcc l | F(9)(32) = 0.92<br>Intensity = 0.00<br>Size = 0 | 0.5178 | 0.7957 |
| AMY r | F(9)(32) = 0.79<br>Intensity = 0.00<br>Size = 0 | 0.6297 | 0.7957 |
| AMY l | F(9)(32) = 0.78<br>Intensity = 0.00<br>Size = 0 | 0.6366 | 0.7957 |
| mPFC | F(9)(32) = 0.67<br>Intensity = 0.00<br>Size = 0 | 0.7330 | 0.8144 |
| NAcc r | F(9)(32) = 0.20<br>Intensity = 0.00<br>Size = 0 | 0.9922 | 0.9922 |

Notes: p-unc = uncorrected p-value, p-FDR = false discovery rate adjusted p-value, ACC = Anterior Cingulate Cortex, AMY = Amygdala, IN = Insula, mPFC = medial prefrontal cortex, NAcc = Nucleus Accumbens, PCC = posterior cingulate cortex, l = left, r = right.

APPENDIX C
TABLES OF EFFECT SIZES

Table C-1. Effect sizes for resting-state functional connectivity from social brain seed region of interest to target region of interest for younger women during placebo condition.

| Seed ROI | Target ROI | beta | T(8) | p-unc | p-FDR |
|---|---|---|---|---|---|
| ACC | AMY l | 0.28 | 4.68 | 0.001588 | 0.006131 |
| | AMY r | 0.36 | 5.18 | 0.000846 | 0.003796 |
| | Brain Stem | 0.10 | 1.62 | 0.143420 | 0.205239 |
| | IN l | 0.65 | 8.33 | 0.000032 | 0.000415 |
| | IN r | 0.64 | 10.85 | 0.000005 | 0.000109 |
| | mPFC | 0.28 | 4.59 | 0.001781 | 0.006567 |
| | NAcc l | 0.30 | 5.19 | 0.000828 | 0.003796 |
| | NAcc r | 0.30 | 5.21 | 0.000808 | 0.003796 |
| | PCC | 0.45 | 6.74 | 0.000147 | 0.001285 |
| AMY l | ACC | 0.28 | 4.68 | 0.001588 | 0.013182 |
| | AMY r | 0.93 | 10.56 | 0.000006 | 0.000313 |
| | Brain Stem | 0.14 | 2.93 | 0.019138 | 0.044124 |
| | IN l | 0.35 | 5.27 | 0.000752 | 0.011138 |
| | IN r | 0.33 | 5.18 | 0.000841 | 0.011138 |
| | mPFC | 0.20 | 2.45 | 0.040027 | 0.077261 |
| | NAcc l | 0.24 | 5.11 | 0.000919 | 0.011138 |
| | NAcc r | 0.17 | 2.68 | 0.027871 | 0.058565 |
| | PCC | 0.08 | 1.06 | 0.321423 | 0.410433 |
| AMY r | ACC | 0.36 | 5.18 | 0.000846 | 0.007022 |
| | AMY l | 0.93 | 10.56 | 0.000006 | 0.000295 |
| | Brain Stem | 0.17 | 3.98 | 0.004077 | 0.017052 |
| | IN l | 0.35 | 4.38 | 0.002351 | 0.012193 |
| | IN r | 0.44 | 5.60 | 0.000509 | 0.005633 |
| | mPFC | 0.18 | 2.23 | 0.055998 | 0.116195 |
| | NAcc l | 0.22 | 3.90 | 0.004531 | 0.017094 |
| | NAcc r | 0.21 | 4.43 | 0.002199 | 0.012170 |
| | PCC | 0.13 | 2.14 | 0.064446 | 0.127358 |
| Brain Stem | ACC | 0.10 | 1.62 | 0.143420 | 0.306192 |
| | AMY l | 0.14 | 2.93 | 0.019138 | 0.088248 |
| | AMY r | 0.17 | 3.98 | 0.004077 | 0.030762 |
| | IN l | 0.17 | 3.08 | 0.015040 | 0.078020 |
| | IN r | 0.20 | 4.44 | 0.002156 | 0.028584 |
| | mPFC | 0.07 | 0.96 | 0.365910 | 0.548667 |
| | NAcc l | 0.12 | 1.90 | 0.094425 | 0.245483 |
| | NAcc r | 0.05 | 1.17 | 0.276772 | 0.468817 |
| | PCC | 0.06 | 0.76 | 0.468009 | 0.651140 |
| IN l | ACC | 0.65 | 8.33 | 0.000032 | 0.000317 |
| | AMY l | 0.35 | 5.27 | 0.000752 | 0.003264 |
| | AMY r | 0.35 | 4.38 | 0.002351 | 0.007651 |
| | Brain Stem | 0.17 | 3.08 | 0.015040 | 0.036183 |
| | IN l | NA | NA | NA | NA |

Table C-1. Continued

| Seed ROI | Target ROI | beta | T(8) | p-unc | p-FDR |
|---|---|---|---|---|---|
| | mPFC | 0.09 | 1.42 | 0.194728 | 0.291215 |
| | NAcc l | 0.32 | 10.91 | 0.000004 | 0.000092 |
| | NAcc r | 0.26 | 3.76 | 0.005562 | 0.014558 |
| | PCC | 0.06 | 0.90 | 0.392414 | 0.485762 |
| IN r | ACC | 0.64 | 10.85 | 0.000005 | 0.000071 |
| | AMY l | 0.33 | 5.18 | 0.000841 | 0.003772 |
| | AMY r | 0.44 | 5.60 | 0.000509 | 0.002560 |
| | Brain Stem | 0.20 | 4.44 | 0.002156 | 0.007781 |
| | IN l | 0.96 | 16.83 | 0.000000 | 0.000009 |
| | mPFC | 0.04 | 0.51 | 0.624596 | 0.710157 |
| | NAcc l | 0.22 | 4.63 | 0.001678 | 0.006631 |
| | NAcc r | 0.17 | 3.16 | 0.013295 | 0.036783 |
| | PCC | 0.08 | 1.08 | 0.313112 | 0.436778 |
| mPFC | ACC | 0.28 | 4.59 | 0.001781 | 0.012856 |
| | AMY l | 0.20 | 2.45 | 0.040027 | 0.107218 |
| | AMY r | 0.18 | 2.23 | 0.055998 | 0.127337 |
| | Brain Stem | 0.07 | 0.96 | 0.365910 | 0.463672 |
| | IN l | 0.09 | 1.42 | 0.194728 | 0.304951 |
| | IN r | 0.04 | 0.51 | 0.624596 | 0.686642 |
| | NAcc l | 0.21 | 3.40 | 0.009344 | 0.043207 |
| | NAcc r | 0.24 | 3.34 | 0.010274 | 0.043207 |
| | PCC | 0.39 | 5.76 | 0.000425 | 0.004707 |
| NAcc l | ACC | 0.30 | 5.19 | 0.000828 | 0.006246 |
| | AMY l | 0.24 | 5.11 | 0.000919 | 0.006633 |
| | AMY r | 0.22 | 3.90 | 0.004531 | 0.023505 |
| | Brain Stem | 0.12 | 1.90 | 0.094425 | 0.211817 |
| | IN l | 0.32 | 10.91 | 0.000004 | 0.000367 |
| | IN r | 0.70 | 8.51 | 0.000028 | 0.001154 |
| | mPFC | 0.21 | 3.40 | 0.009344 | 0.039773 |
| | NAcc r | 0.70 | 8.51 | 0.000028 | 0.001154 |
| | PCC | 0.11 | 2.23 | 0.056014 | 0.149972 |
| NAcc r | ACC | 0.30 | 5.21 | 0.000808 | 0.011172 |
| | AMY l | 0.17 | 2.68 | 0.027871 | 0.112844 |
| | AMY r | 0.21 | 4.43 | 0.002199 | 0.020283 |
| | Brain Stem | 0.05 | 1.17 | 0.276772 | 0.433435 |
| | IN l | 0.26 | 3.76 | 0.005562 | 0.033856 |
| | IN r | 0.17 | 3.16 | 0.013295 | 0.063039 |
| | mPFC | 0.24 | 3.34 | 0.010274 | 0.050160 |
| | NAcc l | 0.70 | 8.51 | 0.000028 | 0.001970 |
| | PCC | 0.11 | 2.09 | 0.069642 | 0.184554 |
| PCC | ACC | 0.45 | 6.74 | 0.000147 | 0.003321 |
| | AMY l | 0.08 | 1.06 | 0.321423 | 0.413614 |
| | AMY r | 0.13 | 2.14 | 0.064446 | 0.137038 |
| | Brain Stem | 0.06 | 0.76 | 0.468009 | 0.541363 |
| | IN l | 0.06 | 0.90 | 0.392414 | 0.478976 |
| | IN r | 0.08 | 1.08 | 0.313112 | 0.412580 |

Table C-1. Continued

| Seed ROI | Target ROI | beta | T(8) | p-unc | p-FDR |
|---|---|---|---|---|---|
| | NAcc l | 0.11 | 2.23 | 0.056014 | 0.125652 |
| | NAcc r | 0.11 | 2.09 | 0.069642 | 0.142723 |

Notes: ACC = Anterior Cingulate Cortex, AMY = Amygdala, IN = Insula, mPFC = medial prefrontal cortex, NAcc = Nucleus Accumbens, PCC = posterior cingulate cortex, l = left, r = right.

Table C-2. Resting-state functional connectivity effect sizes between social brain regions if interest for older women during placebo condition.

| Seed ROI | Target ROI | beta | T(8) | p-unc | p-FDR |
|---|---|---|---|---|---|
| ACC | AMY l | 0.19 | 2.67 | 0.021887 | 0.054449 |
| | AMY r | 0.20 | 3.94 | 0.002307 | 0.008703 |
| | Brain Stem | 0.02 | 0.42 | 0.685909 | 0.795992 |
| | IN l | 0.55 | 7.84 | 0.000008 | 0.000146 |
| | IN r | 0.55 | 6.15 | 0.000072 | 0.000711 |
| | mPFC | 0.29 | 4.44 | 0.000987 | 0.004376 |
| | NAcc l | 0.14 | 3.17 | 0.008957 | 0.025635 |
| | NAcc r | 0.12 | 2.32 | 0.040719 | 0.091343 |
| | PCC | 0.38 | 6.14 | 0.000073 | 0.000711 |
| AMY l | ACC | 0.19 | 2.67 | 0.021887 | 0.083337 |
| | AMY r | 0.63 | 7.19 | 0.000018 | 0.001472 |
| | Brain Stem | 0.05 | 1.05 | 0.317271 | 0.447097 |
| | IN l | 0.15 | 3.14 | 0.009405 | 0.072046 |
| | IN r | 0.14 | 2.50 | 0.029314 | 0.101377 |
| | mPFC | 0.13 | 4.17 | 0.001561 | 0.037022 |
| | NAcc l | 0.05 | 1.21 | 0.252391 | 0.391559 |
| | NAcc r | 0.04 | 1.21 | 0.250696 | 0.391559 |
| | PCC | 0.19 | 3.05 | 0.011053 | 0.076153 |
| AMY r | ACC | 0.20 | 3.94 | 0.002307 | 0.031911 |
| | AMY l | 0.63 | 7.19 | 0.000018 | 0.000981 |
| | Brain Stem | 0.16 | 2.75 | 0.018777 | 0.115442 |
| | IN l | 0.14 | 3.41 | 0.005837 | 0.057941 |
| | IN r | 0.15 | 2.37 | 0.037266 | 0.154656 |
| | mPFC | 0.14 | 2.55 | 0.026950 | 0.140946 |
| | NAcc l | 0.06 | 1.14 | 0.278738 | 0.472149 |
| | NAcc r | 0.02 | 0.57 | 0.583066 | 0.721619 |
| | PCC | 0.15 | 2.57 | 0.026064 | 0.140946 |
| Brain Stem | ACC | 0.02 | 0.42 | 0.685909 | 0.847379 |
| | AMY l | 0.05 | 1.05 | 0.317271 | 0.591763 |
| | AMY r | 0.16 | 2.75 | 0.018777 | 0.148426 |
| | IN l | 0.14 | 2.50 | 0.029296 | 0.190389 |
| | IN r | 0.13 | 2.23 | 0.047190 | 0.261118 |
| | mPFC | -0.13 | -1.98 | 0.073126 | 0.303977 |
| | NAcc l | -0.03 | -0.40 | 0.697860 | 0.847379 |
| | NAcc r | -0.05 | -0.83 | 0.422373 | 0.688482 |
| | PCC | 0.01 | 0.13 | 0.896856 | 0.960504 |
| IN l | ACC | 0.55 | 7.84 | 0.000008 | 0.000142 |
| | AMY l | 0.15 | 3.14 | 0.009405 | 0.023302 |
| | AMY r | 0.14 | 3.41 | 0.005837 | 0.016148 |
| | Brain Stem | 0.14 | 2.50 | 0.029296 | 0.060038 |
| | IN r | 0.87 | 10.41 | 0.000000 | 0.000041 |
| | mPFC | 0.09 | 1.42 | 0.182225 | 0.247946 |
| | NAcc l | 0.17 | 3.44 | 0.005569 | 0.016114 |
| | NAcc r | 0.19 | 3.95 | 0.002268 | 0.007239 |

Table C-2. Continued

| Seed ROI | Target ROI | beta | T(8) | p-unc | p-FDR |
|---|---|---|---|---|---|
| | PCC | 0.10 | 1.75 | 0.107875 | 0.162187 |
| IN r | ACC | 0.69 | 9.35 | 0.000003 | 0.000029 |
| | AMY l | 0.24 | 4.52 | 0.001104 | 0.004072 |
| | AMY r | 0.29 | 4.77 | 0.000753 | 0.002987 |
| | Brain Stem | -0.01 | -0.18 | 0.864328 | 0.939922 |
| | IN l | 1.06 | 13.68 | 0.000000 | 0.000004 |
| | mPFC | 0.06 | 0.92 | 0.380459 | 0.544450 |
| | NAcc l | 0.17 | 2.85 | 0.017267 | 0.042153 |
| | NAcc r | 0.20 | 3.49 | 0.005848 | 0.016455 |
| | PCC | 0.05 | 1.30 | 0.223932 | 0.365137 |
| mPFC | ACC | 0.29 | 4.44 | 0.000987 | 0.012608 |
| | AMY l | 0.13 | 4.17 | 0.001561 | 0.016197 |
| | AMY r | 0.14 | 2.55 | 0.026950 | 0.077133 |
| | Brain Stem | -0.13 | -1.98 | 0.073126 | 0.164040 |
| | IN l | 0.09 | 1.42 | 0.182225 | 0.315098 |
| | IN r | 0.08 | 1.70 | 0.117693 | 0.238851 |
| | NAcc l | 0.17 | 3.68 | 0.003624 | 0.024066 |
| | NAcc r | 0.19 | 2.61 | 0.024457 | 0.075182 |
| | PCC | 0.22 | 3.80 | 0.002923 | 0.021095 |
| NAcc l | ACC | 0.14 | 3.17 | 0.008957 | 0.067583 |
| | AMY l | 0.05 | 1.21 | 0.252391 | 0.524984 |
| | AMY r | 0.06 | 1.14 | 0.278738 | 0.551919 |
| | Brain Stem | -0.03 | -0.40 | 0.697860 | 0.878182 |
| | IN l | 0.17 | 3.44 | 0.005569 | 0.054383 |
| | IN r | 0.19 | 3.68 | 0.003647 | 0.046571 |
| | mPFC | 0.17 | 3.68 | 0.003624 | 0.046571 |
| | NAcc r | 0.54 | 9.00 | 0.000002 | 0.000348 |
| | PCC | 0.12 | 4.95 | 0.000436 | 0.011835 |
| NAcc r | ACC | 0.12 | 2.32 | 0.040719 | 0.160937 |
| | AMY l | 0.04 | 1.21 | 0.250696 | 0.462396 |
| | AMY r | 0.02 | 0.57 | 0.583066 | 0.727736 |
| | Brain Stem | -0.05 | -0.83 | 0.422373 | 0.635535 |
| | IN l | 0.19 | 3.95 | 0.002268 | 0.053779 |
| | IN r | 0.13 | 3.29 | 0.007199 | 0.077536 |
| | mPFC | 0.19 | 2.61 | 0.024457 | 0.115994 |
| | NAcc l | 0.54 | 9.00 | 0.000002 | 0.000348 |
| | PCC | 0.09 | 1.50 | 0.161022 | 0.356395 |
| PCC | ACC | 0.38 | 6.14 | 0.000073 | 0.000864 |
| | AMY l | 0.19 | 3.05 | 0.011053 | 0.029594 |
| | AMY r | 0.15 | 2.57 | 0.026064 | 0.057689 |
| | Brain Stem | 0.01 | 0.13 | 0.896856 | 0.902292 |
| | IN l | 0.10 | 1.75 | 0.107875 | 0.167358 |
| | IN r | 0.10 | 2.04 | 0.065949 | 0.114037 |
| | mPFC | 0.22 | 3.80 | 0.002923 | 0.011414 |
| | NAcc l | 0.12 | 4.95 | 0.000436 | 0.002679 |
| | NAcc r | 0.09 | 1.50 | 0.161022 | 0.220906 |

Notes: ACC = Anterior Cingulate Cortex, AMY = Amygdala, IN = Insula, mPFC = medial prefrontal cortex, NAcc = Nucleus Accumbens, PCC = posterior cingulate cortex, l = left, r = right.

Table C-3. Resting state functional connectivity effect sizes between social brain regions of interest for younger women after intranasal oxytocin administration.

| Seed ROI | Target ROI | beta | T(8) | p-unc | p-FDR |
|---|---|---|---|---|---|
| ACC | AMY l | 0.27 | 8.43 | 0.000007 | 0.000112 |
| | AMY r | 0.34 | 6.20 | 0.000101 | 0.000677 |
| | Brain Stem | -0.05 | -0.77 | 0.461677 | 0.603451 |
| | IN l | 0.65 | 10.11 | 0.000001 | 0.000040 |
| | IN r | 0.69 | 9.35 | 0.000003 | 0.000065 |
| | mPFC | 0.28 | 4.66 | 0.000893 | 0.003530 |
| | NAcc l | 0.32 | 5.98 | 0.000136 | 0.000801 |
| | NAcc r | 0.31 | 5.60 | 0.000226 | 0.001124 |
| | PCC | 0.34 | 10.29 | 0.000001 | 0.000040 |
| AMY l | ACC | 0.27 | 8.43 | 0.000007 | 0.000206 |
| | AMY r | 0.87 | 18.37 | 0.000000 | 0.000001 |
| | Brain Stem | 0.00 | 0.00 | 0.998782 | 0.998782 |
| | IN l | 0.27 | 6.51 | 0.000068 | 0.000756 |
| | IN r | 0.24 | 4.52 | 0.001104 | 0.004953 |
| | mPFC | 0.16 | 1.99 | 0.074517 | 0.122474 |
| | NAcc l | 0.15 | 2.63 | 0.025111 | 0.052765 |
| | NAcc r | 0.20 | 5.63 | 0.000217 | 0.001712 |
| | PCC | 0.28 | 7.59 | 0.000019 | 0.000344 |
| AMY r | ACC | 0.34 | 6.20 | 0.000101 | 0.001402 |
| | AMY l | 0.87 | 18.37 | 0.000000 | 0.000001 |
| | Brain Stem | 0.04 | 1.56 | 0.149060 | 0.233433 |
| | IN l | 0.26 | 4.50 | 0.001146 | 0.006137 |
| | IN r | 0.29 | 4.77 | 0.000753 | 0.004808 |
| | mPFC | 0.22 | 4.15 | 0.001967 | 0.008897 |
| | NAcc l | 0.17 | 3.00 | 0.013264 | 0.032379 |
| | NAcc r | 0.14 | 2.60 | 0.026432 | 0.055542 |
| | PCC | 0.15 | 5.20 | 0.000399 | 0.003682 |
| Brain Stem | ACC | -0.05 | -0.77 | 0.461677 | 0.583865 |
| | AMY l | 0.00 | 0.00 | 0.998782 | 0.998782 |
| | AMY r | 0.04 | 1.56 | 0.149060 | 0.243573 |
| | IN l | -0.03 | -0.58 | 0.575073 | 0.694550 |
| | IN r | -0.01 | -0.18 | 0.864328 | 0.902380 |
| | mPFC | -0.04 | -0.94 | 0.368428 | 0.497131 |
| | NAcc l | 0.01 | 0.19 | 0.851998 | 0.900575 |
| | NAcc r | 0.06 | 1.22 | 0.249756 | 0.363680 |
| | PCC | -0.16 | -2.33 | 0.042317 | 0.115157 |
| IN l | ACC | 0.65 | 10.11 | 0.000001 | 0.000015 |
| | AMY l | 0.27 | 6.51 | 0.000068 | 0.000354 |
| | AMY r | 0.26 | 4.50 | 0.001146 | 0.003805 |
| | Brain Stem | -0.03 | -0.58 | 0.575073 | 0.681872 |
| | IN r | 1.06 | 13.68 | 0.000000 | 0.000003 |
| | mPFC | 0.04 | 0.68 | 0.514408 | 0.642044 |
| | NAcc l | 0.20 | 4.21 | 0.001812 | 0.005569 |
| | NAcc r | 0.21 | 3.31 | 0.007865 | 0.019200 |

Table C-3. Continued

| Seed ROI | Target ROI | beta | T(8) | p-unc | p-FDR |
|---|---|---|---|---|---|
| | PCC | 0.02 | 0.40 | 0.696873 | 0.761058 |
| IN r | ACC | 0.69 | 9.35 | 0.000003 | 0.000029 |
| | AMY l | 0.24 | 4.52 | 0.001104 | 0.004072 |
| | AMY r | 0.29 | 4.77 | 0.000753 | 0.002987 |
| | Brain Stem | -0.01 | -0.18 | 0.864328 | 0.939922 |
| | IN l | 1.06 | 13.68 | 0.000000 | 0.000004 |
| | mPFC | 0.06 | 0.92 | 0.380459 | 0.544450 |
| | NAcc l | 0.17 | 2.85 | 0.017267 | 0.042153 |
| | NAcc r | 0.20 | 3.49 | 0.005848 | 0.016455 |
| | PCC | 0.05 | 1.30 | 0.223932 | 0.365137 |
| mPFC | ACC | 0.28 | 4.66 | 0.000893 | 0.009206 |
| | AMY l | 0.16 | 1.99 | 0.074517 | 0.176712 |
| | AMY r | 0.22 | 4.15 | 0.001967 | 0.013606 |
| | Brain Stem | -0.04 | -0.94 | 0.368428 | 0.576973 |
| | IN l | 0.06 | 0.92 | 0.380459 | 0.578466 |
| | IN r | 0.06 | 0.92 | 0.380459 | 0.578466 |
| | NAcc l | 0.30 | 5.57 | 0.000237 | 0.003549 |
| | NAcc r | 0.30 | 4.52 | 0.001114 | 0.009736 |
| | PCC | 0.33 | 5.12 | 0.000451 | 0.005342 |
| NAcc l | ACC | 0.32 | 5.98 | 0.000136 | 0.002572 |
| | AMY l | 0.15 | 2.63 | 0.025111 | 0.085071 |
| | AMY r | 0.17 | 3.00 | 0.013264 | 0.056723 |
| | Brain Stem | 0.01 | 0.19 | 0.851998 | 0.886498 |
| | IN l | 0.20 | 4.21 | 0.001812 | 0.012531 |
| | IN r | 0.17 | 2.85 | 0.017267 | 0.068247 |
| | mPFC | 0.30 | 5.57 | 0.000237 | 0.003276 |
| | NAcc r | 0.62 | 11.48 | 0.000000 | 0.000074 |
| | PCC | 0.08 | 1.34 | 0.209461 | 0.362193 |
| NAcc r | ACC | 0.31 | 5.60 | 0.000226 | 0.002681 |
| | AMY l | 0.20 | 5.63 | 0.000217 | 0.002681 |
| | AMY r | 0.14 | 2.60 | 0.026432 | 0.081255 |
| | Brain Stem | 0.06 | 1.22 | 0.249756 | 0.370174 |
| | IN l | 0.21 | 3.31 | 0.007865 | 0.035521 |
| | IN r | 0.20 | 3.49 | 0.005848 | 0.029419 |
| | mPFC | 0.30 | 4.52 | 0.001114 | 0.008043 |
| | NAcc l | 0.62 | 11.48 | 0.000000 | 0.000074 |
| | PCC | 0.12 | 2.40 | 0.037046 | 0.101956 |
| PCC | ACC | 0.34 | 10.29 | 0.000001 | 0.000056 |
| | AMY l | 0.13 | 7.47 | 0.000021 | 0.000322 |
| | AMY r | 0.15 | 5.20 | 0. 000399 | 0.002606 |
| | Brain Stem | -0.16 | -2.33 | 0.042317 | 0.090059 |
| | IN l | 0.02 | 0.40 | 0.696873 | 0.776382 |
| | IN r | 0.05 | 1.30 | 0.223932 | 0.331899 |
| | mPFC | 0.33 | 5.12 | 0.000451 | 0.002770 |
| | NAcc l | 0.08 | 1.34 | 0.209461 | 0.330381 |
| | NAcc r | 0.12 | 2.40 | 0.037046 | 0.083103 |

Notes: ACC = Anterior Cingulate Cortex, AMY = Amygdala, IN = Insula, mPFC = medial prefrontal cortex, NAcc = Nucleus Accumbens, PCC = posterior cingulate cortex, l = left, r = right.

Table C-4. Resting state functional connectivity effect sizes between social brain regions of interest for older women after intranasal oxytocin administration.

| Seed ROI | Target ROI | beta | T(8) | p-unc | p-FDR |
|---|---|---|---|---|---|
| ACC | AMY l | 0.27 | 8.43 | 0.000007 | 0.000112 |
| | AMY r | 0.34 | 6.20 | 0.000101 | 0.000677 |
| | Brain Stem | -0.05 | -0.77 | 0.461677 | 0.603451 |
| | IN l | 0.65 | 10.11 | 0.000001 | 0.000040 |
| | IN r | 0.69 | 9.35 | 0.000003 | 0.000065 |
| | mPFC | 0.28 | 4.66 | 0.000893 | 0.003530 |
| | NAcc l | 0.32 | 5.98 | 0.000136 | 0.000801 |
| | NAcc r | 0.31 | 5.60 | 0.000226 | 0.001124 |
| | PCC | 0.34 | 10.29 | 0.000001 | 0.000040 |
| AMY l | ACC | 0.27 | 8.43 | 0.000007 | 0.000206 |
| | AMY r | 0.87 | 18.37 | 0.000000 | 0.000001 |
| | Brain Stem | 0.00 | 0.00 | 0.998782 | 0.998782 |
| | IN l | 0.27 | 6.51 | 0.000068 | 0.000756 |
| | IN r | 0.24 | 4.52 | 0.001104 | 0.004953 |
| | mPFC | 0.16 | 1.99 | 0.074517 | 0.122474 |
| | NAcc l | 0.15 | 2.63 | 0.025111 | 0.052765 |
| | NAcc r | 0.20 | 5.63 | 0.000217 | 0.001712 |
| | PCC | 0.13 | 7.47 | 0.000021 | 0.000352 |
| AMY r | ACC | 0.34 | 6.20 | 0.000101 | 0.001402 |
| | AMY l | 0.87 | 18.37 | 0.000000 | 0.000001 |
| | Brain Stem | 0.04 | 1.56 | 0.149060 | 0.233433 |
| | IN l | 0.26 | 4.50 | 0.001146 | 0.006137 |
| | IN r | 0.29 | 4.77 | 0.000753 | 0.004808 |
| | mPFC | 0.22 | 4.15 | 0.001967 | 0.008897 |
| | NAcc l | 0.17 | 3.00 | 0.013264 | 0.032379 |
| | NAcc r | 0.14 | 2.60 | 0.026432 | 0.055542 |
| | PCC | 0.15 | 5.20 | 0.000399 | 0.003682 |
| Brain Stem | ACC | -0.05 | -0.77 | 0.461677 | 0.583865 |
| | AMY l | 0.00 | 0.00 | 0.998782 | 0.998782 |
| | AMY r | 0.04 | 1.56 | 0.149060 | 0.243573 |
| | IN l | -0.03 | -0.58 | 0.575073 | 0.694550 |
| | IN r | -0.01 | -0.18 | 0.864328 | 0.902380 |
| | mPFC | -0.04 | -0.94 | 0.368428 | 0.497131 |
| | NAcc l | 0.01 | 0.19 | 0.851998 | 0.900575 |
| | NAcc r | 0.06 | 1.22 | 0.249756 | 0.363680 |
| | PCC | -0.16 | -2.33 | 0.042317 | 0.115157 |
| IN l | ACC | 0.65 | 10.11 | 0.000001 | 0.000015 |
| | AMY l | 0.27 | 6.51 | 0.000068 | 0.000354 |
| | AMY r | 0.26 | 4.50 | 0.001146 | 0.003805 |
| | Brain Stem | -0.03 | -0.58 | 0.575073 | 0.681872 |
| | IN r | 1.06 | 13.68 | 0.000000 | 0.000003 |
| | mPFC | 0.04 | 0.68 | 0.514408 | 0.642044 |
| | NAcc l | 0.20 | 4.21 | 0.001812 | 0.005569 |
| | NAcc r | 0.21 | 3.31 | 0.007865 | 0.019200 |

Table C-4. Continued

| Seed ROI | Target ROI | beta | T(8) | p-unc | p-FDR |
|---|---|---|---|---|---|
| | PCC | 0.02 | 0.40 | 0.696873 | 0.761058 |
| IN r | ACC | 0.47 | 5.89 | 0.000232 | 0.001206 |
| | AMY l | 0.07 | 1.32 | 0.218916 | 0.321593 |
| | AMY r | 0.12 | 2.43 | 0.037769 | 0.079362 |
| | Brain Stem | 0.02 | 0.54 | 0.602077 | 0.713891 |
| | IN l | 0.81 | 9.68 | 0.000005 | 0.000155 |
| | mPFC | 0.00 | 0.01 | 0.992603 | 0.992603 |
| | NAcc l | 0.13 | 2.94 | 0.016619 | 0.038855 |
| | NAcc r | 0.06 | 1.23 | 0.248832 | 0.356087 |
| | PCC | -0.07 | -0.98 | 0.351354 | 0.477030 |
| mPFC | ACC | 0.28 | 4.17 | 0.002421 | 0.044657 |
| | AMY l | 0.04 | 0.58 | 0.574794 | 0.797518 |
| | AMY r | 0.08 | 1.47 | 0.176845 | 0.527247 |
| | Brain Stem | -0.07 | -1.31 | 0.223717 | 0.557363 |
| | IN l | 0.04 | 0.58 | 0.574794 | 0.797518 |
| | IN r | 0.00 | 0.01 | 0.992603 | 0.992603 |
| | NAcc l | 0.25 | 4.18 | 0.002390 | 0.044657 |
| | NAcc r | 0.23 | 3.36 | 0.008324 | 0.086364 |
| | PCC | 0.29 | 4.46 | 0.001583 | 0.037537 |
| NAcc l | ACC | 0.11 | 1.56 | 0.153327 | 0.489466 |
| | AMY l | 0.01 | 0.25 | 0.959299 | 0.809043 |
| | AMY r | 0.04 | 0.75 | 0.469658 | 0.803744 |
| | Brain Stem | -0.01 | -0.14 | 0.894256 | 0.959299 |
| | IN l | 0.16 | 3.33 | 0.008741 | 0.100491 |
| | IN r | 0.13 | 2.94 | 0.016619 | 0.148709 |
| | mPFC | 0.25 | 4.18 | 0.002390 | 0.045053 |
| | NAcc r | 0.62 | 10.62 | 0.000002 | 0.000359 |
| | PCC | 0.12 | 2.12 | 0.063012 | 0.348666 |
| NAcc r | ACC | 0.31 | 5.60 | 0.000226 | 0.002681 |
| | AMY l | 0.20 | 5.63 | 0.000217 | 0.002681 |
| | AMY r | 0.14 | 2.60 | 0.026432 | 0.081255 |
| | Brain Stem | 0.06 | 1.22 | 0.249756 | 0.370174 |
| | IN l | 0.21 | 3.31 | 0.007865 | 0.035521 |
| | IN r | 0.20 | 3.49 | 0.005848 | 0.029419 |
| | mPFC | 0.30 | 4.52 | 0.001114 | 0.008043 |
| | NAcc l | 0.62 | 11.48 | 0.000000 | 0.000074 |
| | PCC | 0.12 | 2.40 | 0.037046 | 0.101956 |
| PCC | ACC | 0.34 | 10.29 | 0.000001 | 0.000056 |
| | AMY l | 0.13 | 7.47 | 0.000021 | 0.000322 |
| | AMY r | 0.15 | 5.20 | 0. 000399 | 0.002606 |
| | Brain Stem | -0.16 | -2.33 | 0.042317 | 0.090059 |
| | IN l | 0.02 | 0.40 | 0.696873 | 0.776382 |
| | IN r | 0.05 | 1.30 | 0.223932 | 0.331899 |
| | mPFC | 0.33 | 5.12 | 0.000451 | 0.002770 |
| | NAcc l | 0.08 | 1.34 | 0.209461 | 0.330381 |
| | NAcc r | 0.12 | 2.40 | 0.037046 | 0.083103 |

Notes: ACC = Anterior Cingulate Cortex, AMY = Amygdala, IN = Insula, mPFC = medial prefrontal cortex, NAcc = Nucleus Accumbens, PCC = posterior cingulate cortex, l = left, r = right

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# BIOGRAPHICAL SKETCH

Désirée Lussier-Lévesque received her Master of Science in psychology from the University of Florida in the Spring of 2018. Her research interests are on structural volumetrics and connectivity between regions of the brain involved in socioemotional information processing, such as those in the basal ganglia and limbic system, using magnetic resonance and diffusion tensor imaging. She is particularly interested in adult age and sex differences of the structures and their functional impact on the socioemotional processing and the experience of pain.