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PROCESSING OF SPATIAL INFORMATION IN SOCIAL AND NON-SOCIAL STIMULI BY OPIOID-EXPOSED AND NON-EXPOSED NEWBORNS

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PROCESSING OF SPATIAL INFORMATION IN SOCIAL AND NON-SOCIAL STIMULI BY OPIOID-EXPOSED AND NON-EXPOSED NEWBORNS

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Arts and Sciences
at the University of Kentucky

By

Alyson Jo Hock

Lexington, Kentucky

Director: Dr. Ramesh S. Bhatt, Professor of Psychology

Lexington, Kentucky

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ABSTRACT OF DISSERTATION

PROCESSING OF SPATIAL INFORMATION IN SOCIAL AND NON-SOCIAL STIMULI BY OPIOID-EXPOSED AND NON-EXPOSED NEWBORNS

The ability to process information from faces is important for effective social functioning. Adults are experts at this function. It has been suggested that the encoding of configural spatial relations among facial features (e.g., the distance between the eyes) contributes to this expertise. I investigated the developmental origin of face processing expertise by studying typically developing newborns' sensitivity to the distance between the eyes and between the nose and the mouth in face stimuli. Further, I investigated whether prenatal opioid exposure is associated with neonates' processing of spatial information in social and non-social stimuli. Infants with prenatal opioid-exposure are at risk for several adverse neurobehavioral effects as well as attention and behavioral problems at school age. Research on both humans and animals converges to suggest that prenatal opioid exposure interferes with the development of proper cognitive functions, specifically, memory for spatial information and general attention. However, very little research has examined the association of prenatal opioid exposure to the development of human infants' early cognitive functioning. The current studies use a visual paired-comparison procedure to investigate infants' sensitivity to spatial information on face and non-face images. Both opioid-exposed and non-exposed (typical) infants discriminated subtle spacing changes in face stimuli. However, while non-exposed newborns processed spatial relational information between two non-face objects, opioid-exposed infants failed to exhibit similar sensitivity. Most critically, combined analyses of data of performance on both social and non-social stimuli indicate a general difference in performance such that opioid-exposed infants' novelty preference scores are lower than non-exposed infants' scores. These results indicate differences between opioid-exposed and non-exposed infants' early development and suggests that spatial processing is a mechanism for the compromise of intellectual development.

KEYWORDS: Face Processing, Infant Cognition,
Prenatal Opioid Exposure, Spatial Processing

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________April, 19, 2017______

PROCESSING OF SPATIAL INFORMATION IN SOCIAL AND NON-SOCIAL STIMULI BY OPIOID-EXPOSED AND NON-EXPOSED NEWBORNS

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Chapter 1: Introduction

Spatial information processing is among several nonverbal learning abilities that underlie the skills considered crucial to school readiness and academic success in childhood (Assel, Landry, Swank, Smith, & Steelman, 2003; McGrath & Sullivan, 2002). Furthermore, effective social functioning specifically relies upon processing spatial information in faces as faces are differentiated on the basis of spatial information and provide information about identity, gender, race, and emotion. Research suggests that adults' extensive experience with faces leads to expert processing of faces through the use of critical spatial information (Maurer, Le Grand, & Mondloch, 2002; McKone, 2010; McKone & Robbins, 2011; Mondloch, Le Grand, & Maurer, 2010). Virtually all models of face-processing assume that experience during infancy contributes to the development of this expertise (e.g., Acerra, Burnod, & de Schonen, 2002; Johnson, 2011; Nelson, 2003; Simion, Di Giorgio, Leo, & Bardi, 2011). Consequently, decades of research have been dedicated to understanding face processing and the underlying developmental mechanisms. In particular, newborn infants' face detection and recognition is the focus of an extensive body of research due to the significance of the minimal visual experience accumulated with faces shortly after birth. A fundamental finding from this research is that human newborns prefer to look at schematic or real face images compared to other equally complex stimuli (Goren, Sarty, & Wu, 1975; Johnson, Dziurawiec, Ellis, & Morton, 1991; Macchi Cassia, Turati, & Simion, 2004). Although this early preference for faces is not debated, alternative explanations have been advanced for the mechanisms responsible for newborn face preferences.

Some researchers posit that the mechanisms underlying face perception are

qualitatively different from those underlying most other kinds of object perception (including objects of expertise; see McKone & Robbins, 2011; Robbins & McKone, 2007 for reviews). For example, it has been suggested that infants might be born with an innate representation of the structural form of a face (Johnson, Senju, & Tomalski, 2015; Morton & Johnson, 1991). Thus, the processing of faces is set apart from the processing of other stimuli in that it is a function of some dedicated inborn mechanism. More specifically, Morton and Johnson's (1991) two-process theory states that some information about the basic structure of faces is available to the infant from birth. The first system, CONSPEC, which is thought to innately provide this structure information, biases the input over the first days to months of life by prioritizing orientation to faces. The second system, CONLEARN, builds upon this input and assists in further specialization for other aspects of face processing. Johnson (2011) speculates that CONSPEC may provide a developmental basis, not just for face perception, but also for broader social cognition, thus ensuring appropriate specialization in response to the social and survival-relevant functions of the face.

An alternative theory is that low-level structural preferences that are not necessarily face-specific are responsible for newborn face preferences. In other words, domain-general perceptual biases such as those based on known Gestalt principles found in adults can explain infants' preferences (Simion, Macchi Cassia, Turati, & Valenza, 2001; Simion & Di Giorgio, 2015; Turati, 2004). According to this theory, newborns' most preferred stimulus would involve an up-down asymmetrical pattern with more features in the upper relative to the lower half (i.e., "T"-like stimuli; Macchi Cassia et al., 2004; Simion, Farroni, Cassia, Turati, & Barba, 2002; Turati, Simion, Milani, & Umiltà, 2002) but only when the

pattern is enclosed within a compatibly shaped area such as an oval (Macchi Cassia, Valenza, Simion, & Leo, 2008; Simion et al., 2002; Turati et al., 2002). Thus, the two models differ in the extent to which face processing in newborns is driven by face-specific or general mechanisms. Nevertheless, both face processing theories assume that infants are born with a predisposition to attend to faces or images that have face-like characteristics, and that one's extensive experience with faces after birth drives development.

Additionally, models of face processing have identified several kinds of information that adults use to identify and discriminate among faces. Diamond and Carey's (1986) model assumes that there are two types of information that are critical for face individuation and recognition: featural and relational information. Featural information refers to discrete, commonly identified parts of the face such as the eyes or nose. Relational information includes both first-order relations (gross structural information, such as the fact that the nose is located above the mouth), and second-order relations (the fine spatial relations among features, such as the distance between the eyes or the space between the nose and mouth; Diamond & Carey, 1986; Mondloch, Le Grand, & Maurer, 2002). Most critically, expertise in face processing is associated with the ability to process second-order relations (also referred to as configural information). This claim is supported by research indicating that adults are superior at processing subtle spatial changes in faces than in other objects (e.g., Diamond & Carey, 1986; Robbins & McKone, 2007; Robbins, Nishimura, Mondloch, Lewis, & Maurer, 2010; Tanaka & Farah, 1993; Tsao & Livingstone, 2008; Yovel & Duchaine, 2006).

The possibility that the processing of faces is different from that of objects is also supported by neuroimaging research suggesting that faces have "special" neural

representations in comparison to non-face objects (e.g., Haxby et al., 2011; Kanwisher, 2010; Kanwisher & Yovel, 2006; but see Bilalić, Langner, Ulrich, & Grodd, 2011 for an alternative view). For example, functional magnetic resonance imaging research suggests that there are clusters of neurons that form face-selective regions (e.g., fusiform face area, occipital face area). Additionally, there are face-specific event-related potential responses, such as the N170. The N170 component serves as evidence of a face-specific response because the amplitudes elicited roughly 170 ms after stimulus onset are virtually always larger in response to faces than to non-face objects (Bentin, Allison, Puce, Perez, & McCarthy, 1996; Eimer, 2011; Eimer & Holmes, 2007). Further, neuropsychological studies have shown a double dissociation between specific impairments in the recognition of faces (i.e., prosopagnosia) versus non-face objects (i.e., object agnosia), suggesting that face and object recognition are capable of being selectively damaged (see Duchaine, Yovel, Butterworth, & Nakayama, 2006 for a review). In summary, behavioral, neuroimaging, and neuropsychological evidence supports the proposition that the mechanisms underlying face perception are different from those underlying most other kinds of object perception.

Face Processing Expertise

As mentioned previously, participants exhibit superior sensitivity to configural information in human faces than in other stimuli (e.g., Diamond & Carey, 1986; Robbins et al., 2010), suggesting a strong association between configural information and face processing expertise. For instance, adults are more accurate at processing spacing changes in human faces than in monkey faces (Mondloch, Maurer, & Ahola, 2006) and house stimuli (Leder & Carbon, 2006; Robbins et al., 2010). Robbins and colleagues (2010) reported, for example, that spacing changes have to be four times as large in house stimuli

as in human face stimuli for adults to exhibit the same level of discrimination. Further, Cassia, Turati, and Schwarzer (2011) reported that 4-year-olds rely more on spacing information when discriminating between faces than between cars. Moreover, Zieber and colleagues (2013) found that 5- and 9-month-olds detect spacing changes in faces but fail to detect equivalent changes in house stimuli, indicating that perceptual specialization for face stimuli and the contribution of configural spacing information to this specialization are evident, at least to some extent, by 5 months of age.

In addition to superior processing of face stimuli compared to other objects, adults and infants are also less accurate at identifying inverted compared to upright faces (e.g., Cashon & Holt, 2015; Freire, Lee, & Symons, 2000; Leder, Candrian, Huber, & Bruce, 2001; Rossion, 2008; Valentine, 1988; Yin, 1969), and this deficit has been specifically linked to configural information processing. That is, some studies demonstrate that inversion affects configural information processing more than other types of information processing (e.g., Collishaw & Hole, 2000; Freire et al., 2000). It is thought that the deficit in configural information processing of inverted faces is due to the smaller degree of exposure to inverted compared to upright faces. Based on these findings, some researchers have concluded that configural information is, in fact, related to face-processing expertise because processing this kind of information is superior in the more frequently encountered upright faces than in the less common inverted faces (Freire et al., 2000; but see McKone & Yovel, 2009).

Development of Configural Processing

Most researchers concur that extensive experience with faces in infancy contributes to the development of face processing expertise (e.g., Acerra et al., 2002; Johnson, 2011;

Nelson, 2003; Pascalis & Kelly, 2009; Simion et al., 2011). Researchers are actively exploring just how much experience with faces is necessary for infants to demonstrate at least some evidence of sensitivity to second-order relational information in faces. Many studies indicate that by 5 months of age infants are sensitive to the spatial relations among facial features (Bhatt, Bertin, Hayden, & Reed, 2005; Hayden, Bhatt, Reed, Corbly, & Joseph, 2007; Zieber et al., 2013). Additionally, 3-4-month-olds discriminate between a typical and a spatially altered face when the spacing changes are outside physiognomic norms (Quinn & Tanaka, 2009), following a brief prime (Galati, Hock, & Bhatt, 2016), or with external features like ears and hair removed (Kangas, 2013). In particular, it appears that the presence of external features disrupts younger infants' face processing abilities because attention appears to be drawn out externally rather than to the relevant internal portions of the face (Maurer & Salapatek, 1976; Pascalis, de Schonen, Morton, Deruelle, & Fabre-Grenet, 1995; Rose, Jankowski, & Feldman, 2008; Turati, Macchi Cassia, Simion, & Leo, 2006).

Consistent with 3.5-month-olds' distraction by external facial features, studies with newborn infants have shown that their face recognition abilities appear to be primarily driven by their recognition of outer facial features such as hair and facial contour (Pascalis et al., 1995; Turati et al., 2006); however, newborns can discriminate between facial identities based solely on internal facial features (Turati et al., 2006). To my knowledge, only one previous study has examined configural processing in faces in newborn infants. Leo and Simion (2009) claimed that newborns are sensitive to the fine spatial relations among facial features by documenting the Thatcher illusion. That is, newborns discriminated between an unaltered face and a thatcherized version of the same face (eyes

and mouth inverted) when the stimuli were upright, but not inverted. These results indicate that even newborns may be sensitive to configural information in faces to some extent, yet it is unclear whether this skill also applies to more realistic spatial changes in faces, such as differences in the spacing among facial features that are within physiognomic norms. I addressed this issue in Experiment 1. Moreover, I examined whether there are group differences between opioid-exposed and non-exposed newborns' configural information processing.

Opioids and Potential Mechanisms of Action

Substance use among pregnant women is a growing problem in the United States. The 2012-2013 National Survey on Drug Use and Health reports of the United States found that 5.4% of women, 15-44 years of age, report using illicit drugs during their pregnancy (SAMHSA, 2014). Moreover, between 2000 and 2009, opioid use during pregnancy underwent an estimated 3-4-fold increase (Salihu, Mogos, Salinas-Miranda, Salemi, & Whiteman, 2015). Given this recent and substantial increase in opioid use among pregnant women, it is more important than ever to examine the impact of prenatal opioid exposure on the development of the neonate. However, to my knowledge, research has yet to examine the perceptual functioning of opioid-exposed newborn infants. Therefore, the current studies investigated whether opioid-exposed and non-exposed neonates differ in their processing of spatial information in social and non-social stimuli using a visual discrimination paradigm.

Heroin and other opioids readily cross the blood-brain barrier and placenta; consequently, maternal opioid use during pregnancy is associated with an increased risk for a number of adverse neonatal outcomes. The most common outcome, neonatal

abstinence syndrome (NAS), affects over half of opioid-exposed infants (Finnegan, Connaughton, Kron, & Emich, 1975; Jansson, DiPietro, Elko, & Velez, 2010). NAS is characterized by gastrointestinal, respiratory, autonomic and central nervous system disturbances (Hayes & Brown, 2012). Commonly observed symptoms include irritability, high-pitched crying, tremors, vomiting, diarrhea, and hypertonicity (Johnson, Gerada, & Greenough, 2003). The onset of symptoms often begins within 48 hours of birth, but delayed withdrawal can occur up to 6 days after birth (Abdel-Latif et al., 2006). Infants with NAS often require prolonged hospitalization and medication therapy. While the exact mechanism(s) by which prenatal opioid exposure and opioid withdrawal affect development is not yet fully understood, there are several possibilities. Opioids may influence development by 1) altering the formation of the myelin sheath (Sanchez, Bigbee, Fobbs, Robinson, & Sato-Bigbee, 2008), 2) affecting hormone and neurotransmitter levels (Konijnenberg & Melinder, 2011), or 3) increasing apoptosis in the hippocampus (Schrott, 2014; Wang & Han, 2009). These neurological alterations may explain the cognitive delays observed in opioid-exposed children.

Developmental Consequences of Prenatal Opioid Exposure

The probability of negative outcomes during pregnancy (e.g., preeclampsia, premature labor and rupture of membranes, placental insufficiency, intrauterine growth retardation, and intrauterine death) increases greatly with illicit opioid use during pregnancy (Kaltenbach, Berghella, & Finnegan, 1998). Even if the mother has a successful labor and delivery, neonates are often undersized and at risk for opioid withdrawal. Additionally, due to opioid's ability to cross the blood-brain barrier, changes in neurological myelination and hormone and neurotransmitter expression may result in the

development of cognitive impairments in infancy and childhood (Konijnenberg & Melinder, 2011). For example, opioid-exposed infants and children frequently have significantly poorer motor development (Messinger et al., 2004) and lower language and cognition scores (Beckwith & Burke, 2014). Many of these deficits continue to be documented in older children. For instance, pre and elementary school-aged children show motor and cognitive impairments (Hunt, Tzioumi, Collins, & Jeffery, 2008), inattention, hyperactivity, increased risk for ADHD diagnosis, and deficits in short-term memory abilities (Konijnenberg & Melinder, 2015) compared to non-exposed controls.

Animal models provide converging evidence. Rodents exposed to opioids have impaired learning and memory performance (Steingart, Solomon, Brenneman, Fridkin, & Gozes, 2000; Wang & Han, 2009). For example, Chen and colleagues (2015) examined rats' performance on a novel object recognition task. The animals were habituated to an empty open-field box and subsequently trained with two identical objects placed in the box. During test, one of the familiar training objects was replaced with a novel object. The time spent exploring the familiar and the novel object was recorded. Rat offspring prenatally exposed to opioids demonstrated significantly reduced recognition memory of familiar objects. Moreover, prenatal opioid exposure impaired spatial memory performance in rats as assessed through the symmetrical maze (Slamberová et al., 2001), 8-arm radial maze (Schrott, La'Tonya, & Serrano, 2008), and Morris water maze tasks (Tramullas, Martinez-Cué, & Hurlé, 2008; Wang & Han, 2009; Yanai et al., 1992). Changes in hippocampal mu-opioid receptors (e.g., increased cell death) after prenatal opioid exposure are thought to contribute to such poor spatial and recognition memory (Schindler et al., 2004; Slamberová, Rimanóczy, Bar, Schindler, & Vathy, 2002; Wang &

Han, 2009). In summary, research using animal models suggests that prenatal opioid exposure can produce lasting changes in brain structure and function. These results enhance findings from human clinical samples by documenting specific deficits in recognition and spatial processing. In the following experiments, I examined whether there are differences between opioid-exposed and non-exposed infants' processing of spatial information in face and non-face stimuli.

Chapter 2: Experiment 1

I tested opioid-exposed and non-exposed infants on stimuli in which the spatial relations between facial features (i.e., distance between the nose and mouth) were changed. Faces were used in this experiment because, as noted earlier, they play a significant role in social interactions by providing a wide variety of important information about people, including identity, gender, race, and emotion. As mentioned previously, the ability to process second-order information is associated with face processing expertise in adulthood (e.g., Diamond & Carey, 1986; Robbins et al., 2010). Experiment 1 examined the developmental origin of infants' sensitivity to second-order spatial relations in faces. More specifically, Experiment 1 aimed to extend Leo and Simion's (2009) results and provide a more direct assessment of typically developing infants' configural information processing of faces (i.e., assessment of sensitivity to the distance between the eyes and between the nose and mouth). This parallels tests commonly used in the adult literature (e.g., Maurer et al., 2002; Mondloch et al., 2010) and with older infants (e.g., Bhatt et al., 2005; Hayden et al., 2007b; Kangas, 2013; Zieber et al., 2013). Furthermore, the changes used in this study are more ecologically valid than the previous work (e.g., Leo & Simion, 2009) in that they capture differences in spatial relations among facial features that exist in typical

populations.

Recall that the presence of external features may disrupt younger infants' face processing, as attention is drawn out externally rather than to than to the internal features of the face (Maurer & Salapatek, 1976; Pascalis et al., 1995; Rose et al., 2008; Turati et al., & Leo, 2006). Kangas (2013) directly tested whether removing the external facial features (i.e., hair, neck) enabled 3.5-month-old infants' discrimination of second-order spatial manipulations within physiognomic norms in typical populations. Infants familiarized and tested on stimuli with external facial features failed to exhibit a novelty preference score that was reliably different than chance performance. In contrast, infants familiarized and tested on the same faces without external features exhibited a novelty preference score that was significantly above chance. The results indicate that the absence of external features allowed 3.5-month-olds to attend to the relevant spatial relations among internal features of faces.

Based on Leo and Simion's (2009) results indicating that newborns are sensitive to the Thatcher illusion (an indirect assessment of sensitivity to configural information in faces), it was hypothesized that non-exposed infants would exhibit sensitivity to configural information changes in faces. In contrast, it was expected that opioid-exposed infants would fail to discriminate equivalent changes because opioid exposure has been shown to compromise spatial processing in animals (Slamberová et al., 2001; 2003; Wang & Han, 2009).

Methods

Participants

Sixteen healthy (non-exposed), full-term Caucasian newborns (9 male; *M* = 33.66 hours old; *SD* = 12.72) and 16 full-term Caucasian newborns prenatally exposed to opioids, but otherwise healthy, (7 male; *M* = 222.31 hours old; *SD* = 144.12) participated in this study. Infants were recruited from the University of Kentucky Hospital's Well Baby Nursery and Neonatal Intensive Care Unit (NICU). To be eligible, research participants could not have any known neurological, optical, or auditory impairments. Furthermore, neonates must have reached at least 37-weeks gestational age, weigh at least 2500 grams at birth, have APGAR scores of 7 or greater at both 1 and 5 minutes and the infant's mother must have been at least 18 years old. See Table 2.1 for further enrollment criteria and Tables 2.2-2.3 for demographics and descriptive statistics of the sample. Prenatal opioid exposure was determined by a positive response to either maternal self-report, meconium report or infant/maternal urine reports (Lester et al., 2002; 2003; Noland et al., 2005). Non-exposed controls were selected from women who were identified as drug-free and delivered at the same hospital during the same time period. Infants were only tested if awake and in a quiet, alert state at the start of testing (Brazelton, 1973). Participants were provided compensation ($15 and a small gift such as a bib or baby blanket) for participating. The data from 7 additional non-exposed infants were excluded from the final sample due to position bias (n = 1), failure to maintain the desired state (i.e., crying or falling asleep; n = 4), and failing to sample both test stimuli (n = 2) and the data from additional 4 opioid-exposed newborns were excluded from the final sample due to failure to maintain the desired state.

Stimuli and Measures

The stimuli used in this experiment were color photographs of two male and two female faces obtained from the MacBrain face set (Tottenham et al., 2009; face numbers 06, 09, 21 and 24) and used in Kangas (2013). Using Adobe Photoshop CS, the configural information of each image was manipulated to affect the eye and mouth regions. Specifically, as shown in Figure 1A, the eyes were moved further apart and the mouth was moved down toward the chin, similar to the changes made in many prior studies that have examined configural information processing (e.g., Bhatt et al., 2005; Freire et al., 2000; Galati et al., 2016; Hayden et al., 2007; Mondloch et al., 2010). Alterations made to the faces followed Farkas' (1994) anthropomorphic norms for Caucasian male and female faces such that both the undistorted and spacing-changed faces fell within the normal range for Caucasian faces. For female face 06, the eyes were moved 3.5 mm and the mouth was moved 3 mm, which respectively correspond to changes of 1.15 and .3 standard deviations according to Farkas' (1994) norms. For female face 09, the eyes were moved 2.5 mm (1.09 SD) and the mouth was moved 5 mm (.57 SD). The eyes of male face 24 were moved 6 mm (2.22 SD) and the mouth was moved 3.5 mm (1.85 SD). Finally, the eyes in male face 21 were moved 8.5 mm (1.09 SD) and the mouth was moved 2 mm (.57 SD). The stimuli were the same as in Galati et al. (2016), except that the external features were removed from each face using Adobe Photoshop CS. Anything that fell outside of the jawline and hairline was considered an external feature (e.g., the hair, ears, and neck). The faces were placed on a white square measuring approximately 35.1° vertically and 31.5° horizontally. On average, the four face stimuli subtended approximately 29.8° vertically and 20.1° horizontally.

All mothers completed the Hollingshead Four Factor Index of Socioeconomic Status measure. This survey is designed to measure the social status of the individual based on marital status, employment status, educational attainment, and occupational prestige (Hollingshead, 1975). Education is rated on a 7-point scale that lists highest grade completed, in which higher scores correspond to higher levels of educational attainment. Occupation is rated on a 9-point scale in which higher scores correspond to higher occupational prestige (see Hollingshead manuscript for a more detailed description).

Apparatus and Procedure

The study took place at the University of Kentucky Hospital. The infants sat on a research nurse's lap 30 cm in front of a 50-cm computer monitor. The nurse was instructed to look away from the monitor and not to point to or signal in any way to the infant during the procedure. The monitor was securely fastened to an adjustable arm so it could be properly aligned with each infant's eyes. A video camera, located on top of the monitor, and DVD recorder was used to monitor and record infant's performance for later off-line coding.

Infants were tested exactly as in Kangas (2013) using a visual paired-comparison procedure that is commonly used to study perceptual and cognitive development (Pascalis, de Haan, & Nelson, 2002; Scott & Monesson, 2009; Zieber, Kangas, Hock, & Bhatt, 2015). Each trial began with the presentation of an attention-getter (rapidly alternating colorful shapes) in the center of the monitor. Once the infant oriented toward the attention-getter, the experimenter pressed a button which led to its disappearance and the start of the familiarization trial. During the familiarization trial, two identical images were presented and remained on the screen until the infant accumulated 30 s of looking. An experimenter,

watching the infant via live video, pressed a key whenever the infant looked at either of the images and another key if the infant looked away. The computer program that controlled the experimental session calculated cumulative durations and proceeded to the test trials once the infant accumulated 30 s of familiarization. Immediately following familiarization, infants were tested on two 8-s test trials for a preference between the two images (one of which was familiar and the other novel). During each test trial, the familiar face was paired with a novel face. Test times were elapsed; that is, the 8-s test trial started as soon as the infant's attention was secured and ended 8 seconds later regardless of the infant's looking behavior.

Within each group, the typical and spatially altered stimuli equally often served as the familiarization stimulus. For instance, for half of the opioid-exposed infants, the familiar image was the original unaltered face while for the other half of the opioid-exposed infants, the familiar image was the corresponding spatially altered face. Moreover, the left/right location of the familiar image was counterbalanced across infants and switched location from test trial 1 to test trial 2. The dependent measure was percent preference for the novel pattern across the two test trials.

Infants' look direction and duration were coded offline by a coder blind to the left-right location of the stimuli, with the video playback slowed to 25% of normal speed. Data from 25% of infants were coded by a second coder to check for reliability. The Pearson correlation between the two coders was .88.

Results and Discussion

In accordance with standard practice and protection against inflated error rates and distortions of statistical estimates, an analysis of outlier status using percentiles and

boxplots (Tukey, 1977; using SPSS version 23.0) was conducted and revealed that data from three opioid-exposed infants were outliers. Subsequent analyses of test performance were conducted without these outliers. The mean times required to accumulate 30s of looking during familiarization are presented in Table 2.4. An independent samples *t*-test failed to reveal a significant difference between opioid-exposed and non-exposed infants' the time to accumulate 30 s of looking, $t(27) = 0.54$, $p = .592$. Thus, there was no evidence to suggest differences in the patterns of familiarization between opioid-exposed and non-exposed infants.

Infants' mean novelty preference scores during the test trials are also shown in Table 2.4. To address the question of whether infants discriminate between an unaltered face and a face in which the second-order spatial information has been altered, two single-sample *t*-tests were used to compare opioid-exposed and non-exposed infants' performance with chance (50%). Non-exposed infants exhibited a mean preference score ($M = 61.20$ %; $SE = 4.03$) that was significantly greater than chance, $t(15) = 2.78$, $p = .014$, $d = .69$. Similarly, opioid-exposed newborns exhibited a mean preference score ($M = 59.37$ %; $SE = 2.87$) that was significantly greater than chance, $t(12) = 3.26$, $p = .007$, $d = .90$. Thus, both opioid-exposed and non-exposed infants discriminated subtle spacing changes in faces.

Sample demographics and descriptive statistics for the non-exposed and opioid-exposed newborns are presented in Tables 2.2 and 2.3. Independent samples *t*-tests indicated that several infant and maternal characteristics (e.g., infant age in hours at the time of testing, infant head circumference, maternal education, and maternal SES) were significantly different between the opioid-exposed and the non-exposed samples. Because

maternal education level is a contributing factor to overall maternal SES scores, maternal education was excluded in the following analysis.

To examine whether there were differences in performance between opioid- and non-exposed infants, an analysis of covariance (ANCOVA) with prenatal exposure (non-exposed, opioid-exposed) as a random between-subjects variable and maternal SES, infant age, and infant head circumference as covariates was conducted on infants' novelty preference scores. The group difference between opioid-exposed and non-exposed infants' mean novelty preference scores was non-significant after statistically controlling for maternal SES, infant age, and head circumference, $F(1, 24) = 1.61$, $p = .217$, $\eta_P^2 = .06$. The covariate, infant head circumference, was significantly related to infants' preference scores, $F(1, 24) = 9.39$, $p = .005$, $\eta_P^2 = .28$. There was insufficient evidence to indicate a difference in performance between the two groups.

Experiment 1 extends Leo and Simion's (2009) documentation of newborn infants' sensitivity to spatial information in faces using the Thatcher illusion to a more direct assessment of spatial relational processing in faces. Newborn infants were sensitive to subtle spacing changes between the eyes and between the nose and mouth. These results suggest that soon after birth, infants are already tuned into the spatial relations among features that enables adults to expertly process facial information. Thus, Experiment 1 makes an important contribution to the understanding of cognitive development as it illustrates that either innate tendencies or just a few hours of experience are sufficient for infants to demonstrate sensitivity to information that is critical for developing face-processing expertise. However, I failed to find any group differences as both opioid-

exposed and non-exposed groups of infants similarly processed spatial information in face images.

Chapter 3: Experiment 2

Experiment 2 tested whether newborns' processing of spatial information in face stimuli is subject to an inversion effect by testing opioid-exposed and non-exposed infants on inverted stimuli. An inversion effect is inferred if performance is superior on upright compared to inverted stimuli (e.g., Bertin & Bhatt, 2004; Cashon & Cohen, 2004; Maurer et al., 2002; Yin, 1969). Inversion effects have been utilized in face processing studies to rule out performance based on low-level features, examine participants' knowledge about the canonical orientation of stimuli, and distinguish between different kinds of processing. As discussed earlier, studies have shown that configural processing is more subject to inversion effects than featural processing; thus, inversion effects have been used to infer configural processing (e.g., Bartlett & Searcy, 1993; Carey & Diamond, 1994; Ferguson, Kulkofsky, Cashon, & Casasola, 2009). To examine whether discrimination of the upright face stimuli was based on infants' use of configural information or due to low-level stimulus features, Experiment 2 tested newborns with inverted versions of the face stimuli used in Experiment 1. If newborns in the current experiment exhibit an inversion effect, it would suggest that their performance was based on configural information rather than on low-level image features, and that they are sensitive to the canonical orientation of faces.

Methods

Participants

Sixteen non-exposed, full-term Caucasian newborns (6 male; $M = 33.32$ hours old; $SD = 15.49$) and sixteen full-term Caucasian newborns prenatally exposed to opioids, but

otherwise healthy, (10 male; *M* = 256.85 hours old; *SD* = 214.05) participated in this study. Infants were recruited in a similar manner as Experiment 1. See Table 2.1 for further enrollment criteria and Tables 2.2-2.3 for demographics and descriptive statistics of the sample. The data from 1 additional non-exposed newborn were excluded from the final sample due to failure to sample both test stimuli and the data from 2 additional opioid-exposed newborns were excluded from the final sample due to failure to maintain the desired state (n = 1), and failure to sample both test stimuli (n = 1).

Stimuli, Apparatus, and Procedure

Inverted stimuli were created by rotating by 180 degrees the male and female face images used in Experiment 1 (see Figure 1B). The apparatus and procedure were identical to those used in Experiment 1. Also, as in Experiment 1, performance during the test trials was scored from the video recordings by an observer who was blind to the position of the novel stimulus. A second, naïve observer re-coded the performance of 25% of participants to establish reliability. The Pearson correlation between the two coders was .85.

Results and Discussion

Outlier analyses, carried out in the same manner as in Experiment 1, revealed that the scores of two opioid-exposed infants were outliers. Subsequent analyses of test performance were conducted without these outliers. The mean times required to accumulate 30s of looking during familiarization are presented in Table 2.4. An independent samples *t*-test failed to reveal a difference between opioid-exposed and non-exposed infants, $t(28) = 0.26$, $p = .795$. Thus, there was insufficient evidence to suggest differences in the patterns of familiarization between opioid-exposed and non-exposed newborns.

Infants' mean novelty preference scores during the test trials are shown in Table 2.4. In parallel with Experiment 1, two single sample *t*-tests were conducted to compare opioid-exposed and non-exposed infants' performance against chance (50%). Non-exposed newborns exhibited a mean preference score (M = 50.48%; SE = 2.34) that was not significantly different from chance, $t(15) = 0.20$, p =.841, d = .05. Likewise, opioid-exposed newborns' mean preference score (M = 45.84%; SE = 2.58) was not significantly different from chance, $t(13) = -1.61$, p =.131, d = .43. These results indicate that both opioid-exposed and non-exposed infants failed to discriminate subtle spacing changes in inverted faces.

Sample demographics and descriptive statistics for the non-exposed and opioid-exposed newborns are presented in Tables 2.2 and 2.3. Independent samples *t*-tests indicated that several infant and maternal characteristics (e.g., age in hours at the time of testing, head circumference, birthweight, maternal education, and maternal SES) were significantly different between the opioid-exposed and the non-exposed samples. Because maternal education level is a contributing factor to overall maternal SES scores, maternal education was excluded in the following analyses. In addition, infant birthweight and head circumference were significantly correlated with each other (r = .467); thus, to avoid including highly correlated covariates, infant birthweight was excluded in the following analyses.

An ANCOVA with prenatal exposure (opioid-exposed, non-exposed) as the random between-subjects variable and maternal SES, infant age and infant head circumference as covariates was conducted on infants' novelty preference scores to analyze whether there were differences in performance between opioid- and non-exposed infants.

The main effect of opioid exposure on infants' preference scores was non-significant after statistically controlling for maternal SES, infant age and head circumference, $F(1, 25) = 2.31$, $p = .141$, $\eta_P^2 = .09$. The covariates were not significantly related to infants' preference scores (all p's > .52). Thus, much like in Experiment 1, there was insufficient evidence to indicate a difference in performance between the opioid-exposed and non-exposed groups.

Chapter 4: Experiment 3

The results from Experiments 1 and 2 indicate that there is insufficient evidence to suggest differences between non-exposed and opioid-exposed infants' performance on tests of spatial information processing in face stimuli. It is possible that faces are special and infants' early bias to attend to faces coupled with the evolutionary importance of processing faces override group differences on discrimination of spatial information processing in faces early in life. Therefore, it is important to examine infants' sensitivity to spatial information in non-face stimuli. The use of non-face stimuli may allow for differences between opioid-exposed and non-exposed infants' ability to discriminate changes in spatial relations to emerge because there is less motivation to process and attend to spatial information in basic shapes compared with faces (Gluckman & Johnson, 2013). Moreover, previous research suggests that animacy, associated with social stimuli like faces, affects infants' and adults' perception of objects. In particular, researchers found that infants' best perceptual and cognitive performance is uncovered when investigated with animate (i.e., social) objects and interactions (Legerstee, 1992; Meltzoff, 1985). Given infants' extensive exposure to faces even during the first days of life, it is possible that their animate nature may induce infants to attend to them and process them at a deeper level than other stimuli in their environment. Furthermore, as previously outlined in the

introduction to this manuscript, the mechanisms underlying face perception are thought to be qualitatively different from those underlying other kinds of object perception (McKone & Robbins, 2011; Robbins & McKone, 2007). Thus, while prenatal opioid exposure may not be associated with disruptions in spatial processing in an absolute sense, it is possible that more robust differences in spatial processing between opioid-exposed and non-exposed infants would emerge with non-face stimuli.

Experiment 3 tested infants on a task used by Gava, Valenza, and Turati (2009) in which typically developing infants exhibited sensitivity to various spatial configurations in non-face stimuli. In their study, infants were habituated to a blinking square appearing in one of four locations relative to a vertical bar (e.g., upper left, lower left, upper right, lower right; see Figure 2). Following habituation, newborns were tested with a familiar stimulus paired with a novel stimulus in which the square appeared in a new spatial position. Newborns discriminated left of bar/right of bar spatial relations even when both test stimuli had squares that were displaced equally, in one case maintaining the left/right spatial relational and in the other switching the location. Thus, Gava and colleagues (2009) concluded that typically developing newborns process the spatial location of a blinking square with relation to a vertical landmark in an absolute sense. Experiment 3 used Gava et al.'s (2009) test to examine whether there are differences in opioid-exposed and non-exposed newborns' spatial information processing.

Methods

Participants

Sixteen healthy, full-term Caucasian newborns (6 male; $M = 40.79$ hours old; $SD = 17.24$) and 16 full-term Caucasian newborns prenatally exposed to opioids, but otherwise

healthy, (10 male; *M* = 124.32 hours old; *SD* = 86.22) participated in this study. Infants were recruited from the University of Kentucky Hospital's Well Baby Nursery and NICU. Participant eligibility was determined in the same manner as previous experiments (see Table 2.1 for enrollment criteria and Tables 2.2-2.3 for demographics and descriptive statistics of the sample). The data from 2 additional non-exposed newborns were excluded from the final sample due to failure to maintain the desired state.

Stimuli

The stimuli were the same as those used by Gava et al. (2009). They were composed of a central, vertical white bar (1.4 cm x 9.2 cm; approx. 3° x 18°) and a blinking white square (2.6 cm x 2.6 cm; approx. 5° x 5°), depicted on a black rectangular frame (11.3 cm x 14 cm; approx. 22° x 27°). The white square blinked at a rate of 500 ms. The blinking square was positioned 1.5 cm (3°) on the left (or right) side of the bar, above (or below) an imaginary horizontal midline (see Figure 2). During familiarization, two identical copies of the vertical bar and square were presented, one on each side of the monitor. Infants were familiarized to one of four spatial configurations in which the square appears in the upper left, upper right, lower left, or lower right in reference to the vertical bar. During the test trials, infants were presented with a familiar spatial relation paired with a new spatial relation (i.e., the square appeared in a novel spatial position) side-by-side.

Apparatus and Procedure

The study utilized the same apparatus and procedure used in Experiments 1 and 2. Before every trial, the infant's attention was attracted to the monitor by flashing two rapidly cycling colorful shapes in the middle of the screen. As soon as the infant's attention was secured, the familiarization stimuli appeared in the middle of the monitor and remained

there until the infant accumulated 30 s of total looking time. Once the infant accumulated 30 s of total looking time, the attention-getter reappeared and directed infants' attention to the middle of the monitor again.

The test trials began immediately following familiarization. Infants were tested for a novelty preference during two 20 s test trials, in which the familiarization stimulus was paired with a novel test stimulus. Both test stimuli were presented simultaneously. The left/right position of the novel item during the first test trial was counterbalanced across participants and reversed during the second test trial. Test trial duration was increased from 8 seconds in Experiments 1 and 2 to 20 seconds because previous research with typically developing newborns found discrimination of left/right spatial relations using 20 s test trials (Gava et al., 2009).

Infants' looking behavior was monitored on-line and recorded. Performance during the test trials was scored from the video recordings by an observer who was blind to the position of the novel stimulus. A second, naïve observer re-coded the performance of 25% of participants to establish reliability. The Pearson correlation between the two coders was .88.

Results and Discussion

An outlier analysis revealed that the scores of two non-exposed and one opioid-exposed infants were outliers. The final analyses of test performance were conducted without these scores. The mean times required to accumulate 30s of looking during familiarization are presented in Table 2.4. An independent samples *t*-test failed to reveal a significant difference between opioid-exposed and non-exposed infants, $t(27) = 1.54$, $p =$

.135. Thus, there was no evidence to suggest a difference in the patterns of familiarization between opioid-exposed and non-exposed infants.

Infants' mean novelty preference scores during the test trials are shown in Table 2.4. To investigate whether infants discriminate between the left/right spatial location of a square with relation to a vertical landmark, two single-sample *t*-tests were used to compare opioid- and non-exposed infants' performance with chance (50%). Non-exposed infants exhibited a mean preference score (M = 58.18%; SE = 3.52) that was significantly greater than chance, $t(13) = 2.32$, $p = .037$, $d = .62$. In contrast, opioid-exposed infants' mean preference score (M = 49.94%; SE = 2.92) was not statistically different from chance, $t(14) = -0.02$, $p = .983$, $d = .01$.

Sample demographics and descriptive statistics for the non-exposed and opioid-exposed newborns are presented in Tables 2.2 and 2.3. Independent samples *t*-tests indicated that infant age in hours at the time of testing, maternal education, maternal employment status, and maternal SES were significantly different between the opioid-exposed and the non-exposed samples. Because maternal education and maternal employment are contributing factors to overall maternal SES scores, maternal education and maternal employment were excluded in the following analyses.

An ANCOVA with prenatal exposure (opioid-exposed, non-exposed) as the random between-subjects variable and maternal SES and infant age as covariates was conducted on infants' novelty preference scores to compare performance between opioid- and non-exposed infants. The difference between opioid-exposed infants and non-exposed infants' preference scores was non-significant after statistically adjusting for infant age and maternal SES, $F(1, 25) = 0.86$, $p = .363$, $\eta_P^2 = .03$. The covariates, infant age and maternal

SES were not significantly related to infants' preference scores (p's > .69). Interestingly, when infant age and SES were not included as covariates, the group difference between opioid-exposed and non-exposed newborns was marginally significant, $F(1, 27) = 3.28$, $p = .081$, $\eta_P^2 = .11$. These results indicate that group differences in infant age and maternal SES are contributing to the difference between opioid-exposed and non-exposed infants' detection of changes in spatial relations of non-face objects.

Performance of non-exposed newborns in the current study replicated Gava and colleagues' (2009) work suggesting that non-drug exposed newborns discriminate spatial information that is defined by the positional relations of objects in the environment. In contrast, opioid-exposed infants failed to discriminate changes in spatial location of a square with relation to a vertical bar. These data suggest a difference between opioid-exposed and non-exposed infants' sensitivity to spatial information in non-face stimuli. However, differences in performance were not statistically significant when other factors such as maternal SES and infant age were controlled. Given that there were only 16 infants in each group, it is possible that the lack of evidence of a difference between opioid-exposed and non-exposed infants was due to low power in this experiment. As described next, I examined this possibility by analyzing the combined data from all three experiments.

Chapter 5: Combined Analyses

An a priori power analysis based upon a preliminary study indicated that at least 51 participants per group would be required to detect between-group differences. This sample size was not feasible for any of the individual experiments in my dissertation project. Therefore, it is highly likely that the lack of evidence of group differences observed in

Experiments 1, 2, and 3 was because the individual experiments were under powered. To examine this possibility, I conducted an analysis with pooled data from Experiments 1-3 and with stimulus condition as a fixed between-subjects variable. Specifically, an ANCOVA with exposure (non-exposed, opioid-exposed) and condition (upright face, inverted face, non-face) as between-subjects variables and maternal SES, infant age and infant head circumference as covariates was conducted on infants' novelty preference scores. The group difference between opioid-exposed and non-exposed infants was significant after statistically controlling for maternal SES, infant age and head circumference, $F(1, 14.11) = 10.37$, $p = .006$, $\eta_P^2 = .42$. The main effect of stimulus condition and the interaction between opioid exposure and stimulus condition were non-significant after controlling for maternal SES, infant age, and head circumference, $F(2, 1.89) = 11.93$, $p = .085$, $\eta_P^2 = .93$; $F(2, 79) = 0.58$, $p = .561$, $\eta_P^2 = .02$, respectfully. Thus, on average across stimulus conditions, non-exposed infants' novelty preference scores were greater than opioid-exposed infants' scores, after statistically controlling for maternal SES, infant age, and head circumference. These data suggest that there is an association between prenatal opioid exposure and memory performance on spatial processing tasks.

Chapter 6: General Discussion

Spatial processing is an ability thought to underlie the skills essential for school readiness and academic success in childhood (Assel et al., 2003; McGrath & Sullivan, 2002). Furthermore, the processing of spatial relations (specifically, second-order relations) among facial features is thought to contribute to expert face processing by adults (e.g., Maurer et al., 2002; McKone & Robbins, 2011; Mondloch et al., 2010; Robbins et al., 2010). The current study demonstrates that typically developing newborn infants, only

a few hours old, are more sensitive to this type of spatial information in upright faces than in inverted faces. The current results extend prior findings indicating that 5-month-olds and 3-month-olds are sensitive to second-order spacing information in faces (Bhatt et al., 2005; Kangas, 2013; Galati et al., 2016; Hayden et al., 2007b; Quinn & Tanaka, 2009). Moreover, this study provides preliminary support for group differences between opioid-exposed and non-exposed newborns' spatial information processing. Non-exposed (typical) newborns discriminated changes in spatial relations in non-face stimuli while opioid-exposed newborns failed to exhibit sensitivity to spatial changes in these non-face stimuli. Additionally, when examining data from all three experiments, opioid-exposed infants' novelty preference scores were, on average, lower than non-exposed infants' scores after statistically adjusting for maternal SES, infant age, and head circumference. In the following discussion, I first focus on the performance of non-exposed newborns and the unique contribution of the study to the existing literature on the typical development of newborns' face processing. Second, I discuss the group differences between opioid-exposed and non-exposed newborn infants' processing of spatial relations in face and non-face stimuli.

Previous research has documented the development of sensitivity to spatial information in faces at 3 months of age. In the current study, newborns, with only hours of experience with human faces, demonstrated sensitivity to second-order relations in faces. Why would newborns be sensitive to such information in faces? Morton and Johnson's (1991; 2015) model would explain newborns' performance as being driven by an innate mechanism. The possibility that newborns' performance is driven by an innate (or at the very least a rapid learning mechanism) is in agreement with Zieber and colleagues' (2013)

findings indicating that young infants detect comparable spatial changes in both human and monkey faces in spite of the fact that infants have little to no exposure to monkey faces. Thus, one might conclude that direct exposure is not a prerequisite for the ability to process second-order spatial information.

Further substantiation for the idea that extensive experience is not necessary to process second-order spatial information comes from the fact that, unlike some previous research (e.g., Quinn, Yahr, Kuhn, Slater, & Pascalis, 2002; Ramsey, Langlois, & Marti, 2005; Ramsey-Rennels & Langlois, 2006), infants in the current study did not exhibit differences in the processing of female versus male faces even though female faces likely comprise the majority of infants' limited experience with faces. This supports the notion of a more general mechanism dedicated to processing faces as well as other stimuli. This mechanism may subsequently become "tuned" to the more experienced faces, as a direct consequence of the exposure (Scott & Monesson, 2010). For example, newborns do not respond differentially to the gender of faces (current study; Quinn et al., 2008), but 3-month-old infants prefer to look at female faces over male faces and discriminate between female faces more readily than between male faces (e.g., Quinn et al., 2002; Ramsey et al., 2005; Ramsey-Rennels & Langlois, 2006; Rennels, Kayl, Langlois, Davis, & Orlewicz, 2016). Similar developmental patterns of specialization or perceptual narrowing have been documented for race (e.g., Hayden, Bhatt, Joseph, & Tanaka, 2007; Hayden, Bhatt, Kangas, Zieber, & Joseph, 2012; Hayden, Bhatt, Zieber, & Kangas, 2009; Kelly et al., 2007; Quinn, Lee, Pascalis, & Tanaka, 2015) and species (e.g., de Haan, Johnson, & Halit, 2003; Pascalis et al., 2002).

Recall that Leo and Simion (2009) concluded that newborns are sensitive to the fine spatial relations among facial features, a skill associated with expert face processing, by documenting the Thatcher illusion in newborn infants. However, the Thatcher illusion may not be directly tied to second-order processing (Psalta, Young, Thompson, & Andrews, 2014) and at best is an indirect measure of the processing of second-order spatial relations in faces. The current study goes beyond this previous research by directly assessing newborn infants' sensitivity to the distance between the eyes and between the nose and mouth. This test of spatial information processing in faces paralleled those used with adults (e.g., Maurer et al., 2002; Mondloch et al., 2010) and older infants (Bhatt et al., 2005; Galati et al., 2016; Hayden et al., 2007b; Kangas, 2013; Zieber et al., 2013). Additionally, the second-order spatial changes tested in the current study are more ecologically valid than the Thatcherized faces used previously as they capture subtle spatial differences that exist within the typical population and as such give a better picture of face processing skills used in everyday life, such as identification. It is important to note, however, the ecological validity of the stimuli used in the current study may be challenged by the fact that the face images do not include external features such as ears or hair. Recall that Kangas (2013) found a difference between performance on faces with and without external facial features at 3.5 months of age. That is, 3.5-month-old infants are sensitive to configural information in faces without external facial features (Kangas, 2013) but do not readily process second-order spacing changes in the presence of external features (Galati et al., 2016; Kangas, 2013). Therefore, it is unlikely that newborns would be sensitive to configural information with external features present.

An additional key finding in this study is that newborn infants discriminate spatial changes in upright but not inverted faces. As previously described, the inversion effect refers to performance impairments on inverted compared to upright stimuli (Bertin & Bhatt, 2004; Cashon & Cohen, 2004; Maurer et al., 2002; Yin, 1969) and is considered a critical marker of configural face processing (Bartlett & Searcy, 1993; Cashon & Holt, 2015; Carey & Diamond, 1994; Ferguson et al., 2009). Most of the previous work involving newborn infants and processing of inverted face stimuli examined the nature of face preferences at birth (Johnson et al., 1991; Mondloch et al., 1999; Macchi Cassia et al., 2004; Slater, Quinn, Hayes, & Brown, 2000; Valenza, Simion, Cassia, Umiltà, 1996); however, a few studies have observed superior recognition of upright compared to inverted faces shortly after birth (Turati et al., 2006; Leo & Simion, 2009). For example, Turati and colleagues (2006) found that face recognition was disrupted by inversion when the inner portions of the face were presented, but not when the full face or just the outer features were presented. The present results extended the face inversion effect to the processing of configural information as newborns discriminated second-order spatial changes in upright, but not inverted face stimuli.

Another goal of the present study was to investigate whether there are differences between opioid-exposed and non-exposed newborn infants' processing of spatial relations in face and non-face stimuli. The results of Experiment 1 indicated that, like the non-exposed newborns, opioid-exposed newborns discriminated between an unaltered face and a spatially altered face when tested with upright but not inverted images. Additionally, there was insufficient evidence to suggest that opioid-exposed newborn's sensitivity to spatial information in faces was different from that of non-exposed newborns. Thus, under

the procedural and stimulus conditions of Experiment 1, prenatal opioid exposure was not associated with newborn infants' sensitivity to configural information in face stimuli. In contrast, the initial analysis of data from Experiment 3 demonstrated that opioid exposed infants failed to discriminate changes in left/right spatial relations in non-face stimuli while non-exposed infants discriminated the same spatial changes. The group difference between non-exposed and opioid-exposed infants was marginally significant; however, this difference became non-significant once factors such as infant age and maternal SES were statistically controlled. This suggests that infant age and maternal SES were contributing to differences between opioid-exposed and non-exposed newborns' spatial processing of non-face stimuli in Experiment 3, and this is consistent with previous research (e.g., Frank et al., 2002; Messinger et al., 2004). Note however, that when data from all three experiments were combined to generate sufficient power, non-exposed infants' mean novelty preference score was greater than opioid-exposed infants' score, after statistically controlling for maternal SES, infant age, and head circumference. This important finding suggests an association between prenatal opioid exposure and performance on spatial processing tasks.

The existing literature on the early cognitive development of opioid-exposed infants is limited; nevertheless, it suggests that opioid exposed infants' performance differs from non-exposed infants in a manner that is consistent with current findings. For instance, two-month-old NAS infants' mean composite scores on language and cognition subscales of the Bayley-III were significantly lower than scores of the general corresponding population (Beckwith & Burke, 2014). Furthermore, infants exposed to opioids had significantly lower mental developmental index scores on the Bayley than non-exposed

infants at 18 months of age (Hunt et al., 2008) and at 8 months of age (Salo et al., 2010). The results of the current study extend the previous research by documenting group differences in cognitive performance of infants only hours old.

One nuance to the group difference is that both opioid-exposed and non-exposed infants' mean novelty preference scores were significantly different from chance in Experiment 1, indicating that even opioid-exposed infants discriminated subtle second-order spacing changes in faces. A comparable pattern has been reported by some previous research in which opioid-exposed infants' scores are significantly different from controls but fall within the normal range (Bunikowski, Grimmer, Heiser, Metze, Schafer, & Obladen, 1998; Lifschltz & Wilson, 1991). Moreover, recall that there was insufficient power to detect between group differences in Experiment 1. In contrast, each experiment was sufficiently powered to detect differences from chance.

While the present data indicate subtle differences in performance between opioid and non-exposed infants, this research was not without limitations. The limitations reflect the difficulties in matching groups for studies of prenatal drug exposure and in accuracy of recall and truthful disclosure of illegal activity during pregnancy. These measurement difficulties may have led to incomplete ascertainment and evaluation of both licit and illicit drugs during pregnancy. Further, it is difficult to disentangle the role of prenatal opioid exposure on neonates' cognitive development from other prenatal and environmental characteristics. Although all infants met minimum enrollment criteria (see Table 2.1), there was still heterogeneity within the sample on other variables. For instance, the opioid-exposed and non-exposed groups differed significantly on various infant and maternal characteristics (Tables 2.2-2.3). This is consistent with previous research that has also

documented differences in infant birth weight (Clearly et al., 2012; Lejeune, Simmat-Durand, Gourarier, & Aubisson, 2006), head circumference (Brown et al., 1998; Welle-Strand et al., 2013), and measures of family socioeconomic status (Hans, 1989; Hans & Jeremy 2001; Kolar, Brown, Haertzen, & Michaelson, 1994) between opioid-exposed and non-exposed controls.

It is also important to remember that these data are correlational in nature. As a result, one cannot draw definitive conclusions regarding prenatal opioid exposure causing differences in infants' mean novelty preference scores. Given that it is unethical to randomly assign participants to prenatal opioid exposure conditions there is no way of knowing that the covariates measured and used in the analyses in the current study were the only important ones between groups when multiple differential selection factors may have been operating (Maxwell & Delaney, 2004). For example, there may be group differences in the quality of the infant-parent relationship and postnatal environment. Previous research indicates that the interactions between an infant and their primary caretaker is instrumental in the development of behavior and emotion regulation, social skills, and cognitive ability (Morris, Silk, Steinberg, Myers, & Robinson, 2007; Scaramella & Leve, 2004). These factors are exceptionally important within the context of prenatal drug exposure as opioid abusing mothers show a decreased ability to manage their pregnancies, identify their infant's cues after birth, and to respond appropriately to them (Hans, 2002). It is likely that prenatal and infant characteristics along with the complex interactions of social, psychological, and physical variables involved during pregnancy have a collective impact on infants' cognitive development.

Furthermore, it is especially important to consider the variability within the opioid-exposed sample because there were differences in the type of opioid, presence/absence of poly-drug use, amount/duration of opioid use, opioid maintenance therapy compliance, etc. between experiments. For instance, 9/13 mothers of infants in Experiment 1 were in a Subutex program (buprenorphine) and compliant versus 5/15 mothers of infants tested in Experiment 3. The current study was not designed to examine different patterns of visual preference performance across various types of opioid exposure; however, upon post hoc examination of the upright face data, the 9 infants of mothers who reportedly only used buprenorphine during pregnancy had a higher mean novelty preference score (M = 59.10; SE = 6.92) than infants of mothers who either used other illicit opioids or buprenorphine in addition to other licit/illicit substances (M = 45.23; SE = 11.29). Additional research projects examining the effect of various types of opioid exposure on infants' novelty preference scores and comparing sensitivity to spatial relations for face and non-face stimuli within the same participants are needed. Moreover, research with larger sample sizes and more comprehensive measures of prenatal, infant, and maternal characteristics needs to be completed. Examples of these measures include but are not limited to: access to/amount of prenatal care, maternal nutrition, nursery environment (e.g., NICU, versus mother-baby, versus, newborn nursery), parental time at bedside, and any other non-pharmacological interventions being utilized (e.g., swaddling, kangaroo care, massage therapy, essential oils, music therapy).

Moreover, a complete understanding of the development of spatial processing will require the examination of the processing of many different kinds of spatial information across a variety of stimulus and procedural conditions. Additionally, it is possible that

group differences in spatial information processing become more robust later in development. Future research should aim to examine the development of sensitivity to spatial information in cohorts of opioid-exposed and non-exposed infants longitudinally to examine this possibility.

To my knowledge, this dissertation project is the first to compare non-exposed and opioid-exposed newborn infants' early cognitive functioning using a visual-paired comparison task. Because this visual preference task is non-invasive, can be applied with ease, and is reliable across multiple time points within the first year of life, I think that this study is a promising first step toward the creation of an early assessment for infants that may be considered as belonging to an at-risk population. This study documents important perceptual group differences that could directly inform interventions designed to be implemented during a time when the developing neural system is highly plastic.

In conclusion, the current study demonstrates that both non-exposed and opioid-exposed newborn infants are sensitive to subtle spatial changes in upright face stimuli. Discrimination of this type of spatial change in face stimuli suggests that, hours after birth, infants are already paying attention to the spatial relations among features that enables adults to be expert face processors. Moreover, across all experimental conditions, opioid-exposed newborns exhibited novelty preference scores that were lower than the scores of non-exposed newborns after statistically adjusting for maternal SES, infant age, and head circumference. Thus, there appears to be an association between prenatal opioid exposure and the compromising of memory for spatial information.

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Table 2.1. Enrollment Criteria

Non-exposed	**Opioid-exposed**
1) Gestational age ≥ 37 weeks	1) Gestational age ≥ 37 weeks
2) APGAR score of ≥ 7 at both 1 and 5 minutes	2) APGAR score of ≥ 7 at both 1 and 5 minutes
3) Birth weight ≥ 2500 baby grams	3) Birth weight ≥ 2500 baby grams
4) Maternal age ≥ 18 years of age	4) Maternal age ≥ 18 years of age
5) < 4 days postnatal age	5) < 4 days postnatal age
6) No seizures	6) No seizures
7) No major congenital malformations	7) No major congenital malformations
8) No known auditory, neurological or optical impairments	8) No known auditory, neurological or optical impairments
9) Not unlikely to survive	9) Not unlikely to survive
10) No blood pressure instability	10) No blood pressure instability
11) No known prenatal drug exposure (mother admitting to use, has positive drug screen during pregnancy or delivery, or positive infant urine or meconium test)	11) Known prenatal opioid exposure (mother admitting to use, has positive drug screen during pregnancy or delivery, or positive infant urine or meconium test)
12) No major medical condition(s).	12) No major medical condition(s)
13) Informed consent	13) Informed consent

Table 2.2. Characteristics of Biological Mothers in the Opioid-Exposed and Non-Exposed Groups

	Mean (*SD*)/ Number (%)		
	Opioid-exposed	Non-exposed	*p*-value
Experiment 1			
Education	4.19 (0.75)	5.63 (1.41)	.001
Employment	1 (6.3%)	6 (37.5%)	.087
SES Hollingshead	18.81 (6.05)	32.50 (17.80)	.007
Age (yr)	27.13 (5.48)	28.88 (5.68)	.382
Experiment 2			
Education	4.38 (0.89)	5.88 (1.36)	.001
Employment	3 (18.8%)	9 (56.3%)	.068
SES Hollingshead	20.94 (10.43)	40.44 (21.00)	.002
Age (yr)	26.81 (5.01)	29.75 (6.43)	.160
Experiment 3			
Education	4.19 (0.91)	6.00 (1.03)	<. 001
Employment	6 (37.5%)	16 (100%)	<. 001
SES Hollingshead	20.38 (6.22)	49.56 (14.05)	<. 001
Age (yr)	27.56 (4.05)	31.19 (6.02)	.055
Total			
Education	4.25 (0.84)	5.83 (1.26)	< .001
Employment	10 (20.8%)	31 (64.6%)	< .001
SES Hollingshead	20.04 (7.72)	40.83 (18.83)	< .001
Age (yr)	27.17 (4.79)	29.94 (6.00)	.014

*Note: demographics and descriptive statistics were examined for statistical group differences using independent samples *t*-tests for continuous variables and Pearson's chi-squared tests for categorical variables.

Table 2.3. Birth Characteristics of Opioid-Exposed and Non-Opioid-Exposed Infants

	Mean (*SD*)/ Number (%)		
	Opioid-exposed	**Non-exposed**	*p*-value
Experiment 1	n =16	n =16	
Age (hours)	222.31 (144.12)	33.66 (12.72)	< .001
Birth Weight (g)	3198.13 (521.48)	3474.38 (396.58)	.102
Head circumference (cm)	33.77 (1.42)	35.22 (1.01)	.002
Gestational age	39.42 (1.03)	39.23 (1.07)	.611
Apgar 1 minute	8.44 (0.63)	8.56 (0.73)	.607
Apgar 5 minute	8.88 (0.34)	8.84 (0.44)	.823
Infant Sex	7 male (43.8%)	9 male (56.3%)	.724
Experiment 2	n =16	n =16	
Age (hours)	263.64 (216.87)	33.33 (15.49)	< .001
Birth Weight (g)	3144.81 (410.71)	3504.06 (504.96)	.035
Head circumference (cm)	33.59 (1.28)	35.17 (1.40)	.002
Gestational age	39.43 (1.05)	39.75 (1.04)	.390
Apgar 1 minute	8.13 (0.72)	8.44 (0.73)	.231
Apgar 5 minute	8.94 (0.25)	9.00 (0.00)	.325
Infant Sex	10 male (62.5%)	6 male (37.5%)	.289
Experiment 3	n =16	n =16	
Age (hours)	124.32 (86.22)	40.79 (17.24)	.001
Birth Weight (g)	3153.38 (500.92)	3334.25 (426.98)	.280
Head circumference (cm)	33.98 (1.51)	34.66 (1.39)	.196
Gestational age	39.08 (0.90)	39.08 (0.99)	.979
Apgar 1 minute	8.50 (0.52)	8.44 (0.73)	.781
Apgar 5 minute	8.94 (0.44)	8.88 (0.50)	.711
Infant Sex	10 male (62.5%)	6 male (37.5%)	.289
Total	n =48	n =48	
Age (hours)	203.42 (165.82)	35.93 (15.34)	< .001
Birth Weight (g)	3165.44 (470.39)	3437.56 (442.00)	.004
Head circumference (cm)	33.78 (1.39)	35.02 (1.28)	< .001
Gestational age	39.31 (0.99)	39.35 (1.05)	.824
Apgar 1 minute	8.35 (0.64)	8.48 (0.71)	.367
Apgar 5 minute	8.92 (0.35)	8.91 (0.38)	.889
Infant Sex	27 male (56.3%)	21 male (43.8%)	.307

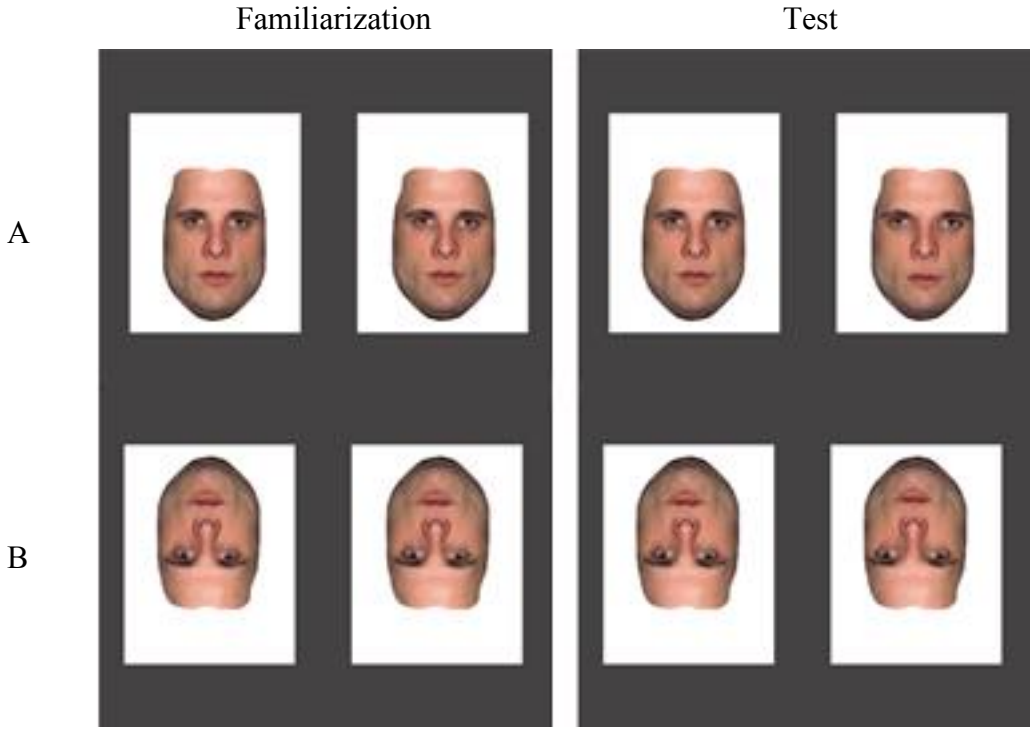
*Note: demographics and descriptive statistics were examined for statistical group differences using an independent samples *t*-test for continuous variables and Pearson's chi-squared tests for categorical variables.

Table 2.4. Mean (and Standard Error) Time to Accumulate 30 s of Familiarization and Novelty Percent Preferences.

	n	Mean Time to Accumulate 30 s Looking	Mean Novel Looking Time (s)	Mean Familiar Looking Time (s)	Mean Novelty Preference (%)	*t* (versus chance)
Experiment 1						
Non-exposed	16	40.69 (3.51)	5.85 (0.73)	3.62 (0.52)	61.20 (4.03)	2.78*
Opioid-exposed	13	44.89 (7.47)	6.99 (0.52)	4.73 (0.37)	59.37 (2.87)	3.26*
Experiment 2						
Non-exposed	16	37.09 (3.46)	4.60 (0.42)	4.33 (0.34)	50.48 (2.34)	0.20
Opioid-exposed	14	38.89 (6.22)	5.33 (0.58)	6.18 (0.60)	45.84 (2.58)	-1.61
Experiment 3						
Non-exposed	14	46.14 (5.96)	13.79 (1.71)	9.60 (1.36)	58.18 (3.52)	2.32*
Opioid-exposed	15	36.71 (2.01)	14.31 (0.90)	15.06 (1.34)	49.94 (2.92)	-0.02

Note: * $p < .05$

Figure 1. Sample of the stimuli used in Experiments 1 and 2.

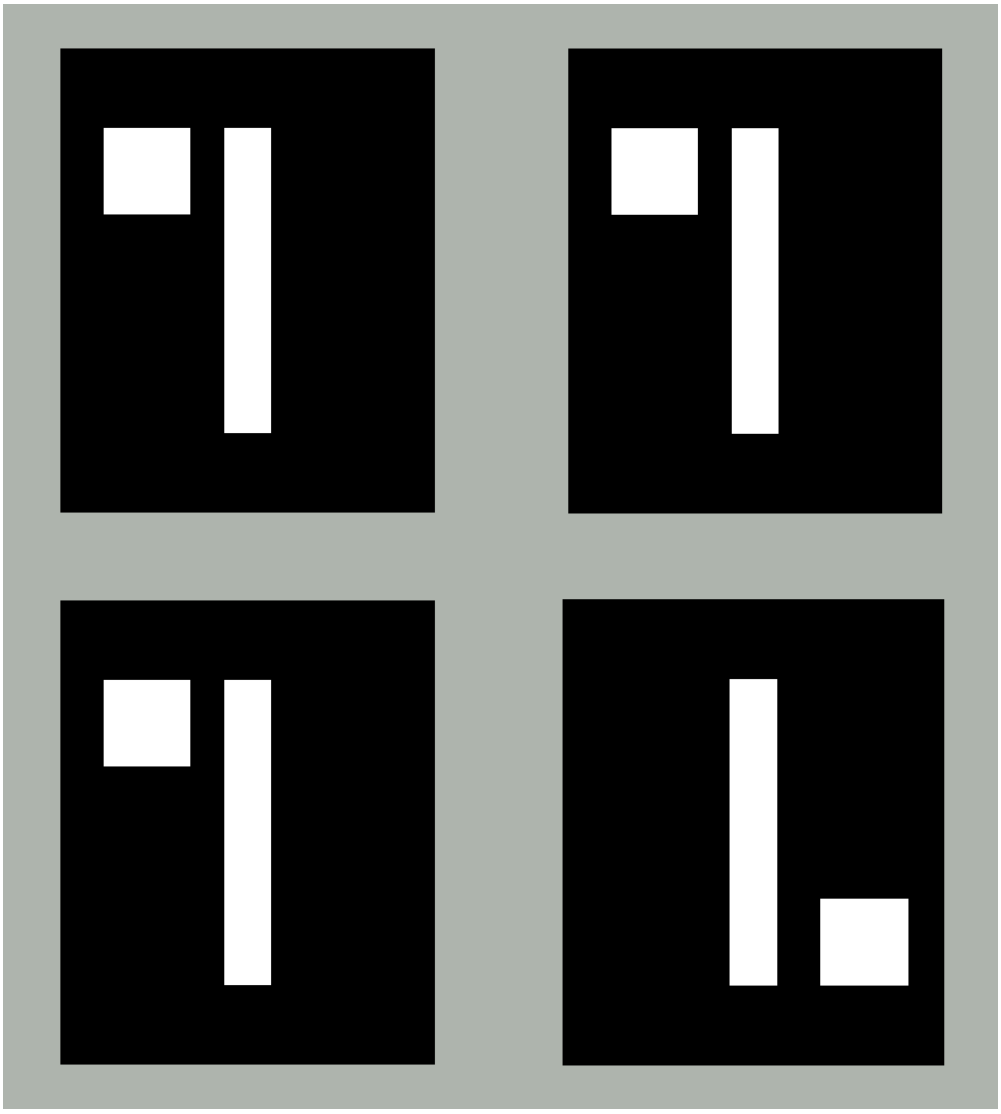


Note. Familiarization stimuli are presented in the left column and test stimuli are presented in the right column with the familiar spatial configuration on the left side and the novel spatial configuration on the right side. Row (A) depicts an example of upright face stimuli, row (B) inverted face stimuli.

Figure 2. Sample of the non-face stimuli used in Experiment 3.

A

B



Note. Row (A) depicts an example (upper-left spatial position of the square) of stimuli during familiarization when two identical stimuli are presented to the infants. Row (B) is an example of the test stimuli. The left image depicts the familiar spatial configuration while the right image is novel. The white square blinked at a rate of 500 ms in an attempt to increase attention toward the element that changes spatial location, enhancing infants' ability to detect the change in spatial relation. The white square appeared in 1 of 4 locations during familiarization and this location was counterbalanced across infants.

ALYSON J. HOCK

Vita

Education

Ph.D.	Experimental Psychology: Cognitive and Developmental Sciences April, 2017 Dissertation: *"Processing of spatial information in social and non-social stimuli by opioid-exposed and non-exposed newborns"* University of Kentucky, Lexington, KY Advisor: Dr. Ramesh S. Bhatt, Ph.D.
M.S.	Experimental Psychology December, 2013 Thesis: *"The whole picture: Body posture recognition in infants"* University of Kentucky, Lexington, KY Advisor: Dr. Ramesh S. Bhatt, Ph.D.
B.A.	Psychology and Biochemistry May, 2011 Simpson College, Indianola, IA Summa Cum Laude

Professional Positions

2011 – Present	Research Assistant, Department of Psychology, University of Kentucky
2011 – Present	Teaching Assistant, Department of Psychology, University of Kentucky

Scholastic and Professional Honors

2016	Provost's Award for Outstanding Teaching
2016	College of Arts and Sciences Certificate for Outstanding Teaching
2016	Certificate for Outstanding Developmental Graduate Student
2012-2017	Research Challenge Trust Fund (RCTF) Travel Award
2015	Certificate for Outstanding Developmental Graduate Student
2012-2016	University of Kentucky Graduate School Travel Award
2014	International Congress on Infant Studies Student Travel Award
2013	Society for Research in Child Development Student Travel Award
2011	Graduate School Academic Year Non-service Fellowship

Professional Publications

Peer-Reviewed Manuscripts

Hock, A., Oberst, L., Jubran, R., White, H., Heck, A., & Bhatt, R.S. (2017). Integrated emotion processing in infancy: Matching of faces and bodies. *Infancy.*

Heck., A., **Hock, A.,** White., H., Jubran, R., & Bhatt, R.S. (2017). Further evidence of early development of attention to dynamic facial emotions: Reply to Grossmann and Jessen (2016). *Journal of Experimental Child Psychology, 153*(1), 155-162.

Galati, A., **Hock, A.,** & Bhatt, R.S. (2016). Perceptual learning and face processing in infancy. *Developmental Psychobiology, 58*(7), 829-840.

Heck., A., **Hock, A.,** White., H., Jubran, R., & Bhatt, R.S. (2016). The development of attention to dynamic facial emotions. *Journal of Experimental Child Psychology, 147*(1), 100-110.

Bhatt, R.S., **Hock, A.,** White, H., Jubran, R., Kangas, A. (2016). The development of body structure knowledge in infancy. *Child Development Perspectives, 10*(1), 45-52.

Hock, A., White, H., Jubran, R., & Bhatt, R.S. (2016). The whole picture: Holistic body posture recognition in infancy. *Psychonomic Bulletin & Review*, *23*, 426-431.

Hock, M.F., Brasseur-Hock, I.F., **Hock, A.,** Konrardy, B. (2015). The effects of a comprehensive reading program on reading outcomes for middle school students with disabilities. *The Journal of Learning Disabilities,*1-18.

Hock, A., Kangas, A., Zieber, N., & Bhatt, R.S. (2015). The development of sex category representation in infancy: Matching of faces and bodies. *Developmental Psychology, 51*(3), 346-352.

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Zieber, N., Kangas, A., **Hock, A.,** & Bhatt, R.S. (2014). The development of intermodal emotion perception from bodies and voices. *Journal of Experimental Child Psychology, 126*, 68-79.

Zieber, N., Kangas, A., **Hock, A.,** & Bhatt, R. S. (2014). Infants' perception of emotions from body movements. *Child Development*, *85*(2), 675-684.

Zieber, Z., Kangas, A., **Hock, A.,** Hayden, A., Collins, R., Bada, H, Joseph, J., & Bhatt, R.S. (2013). Perceptual specialization and configural face processing in infancy. *Journal of Experimental Child Psychology, 116*(3), 625-639.

Manuscripts under Peer Review

Hock, A., White, H., Heck, A., Jubran, R., Galati, A., & Bhatt, R.S. (under review). Categorical perception of facial emotions in infancy.

Jubran, R., White, H., **Hock, A.,** Heck, A., & Bhatt, R. S. (under review). Body part structure knowledge in infancy: It's hand-y!.

Presentations in Professional Meetings

Hock, A., & Bhatt, R.S. (2017). *Visual scanning of body emotions in infancy.* The Society for Research in Child Development, Austin, TX. April 5-7, 2017 (poster presentation).

Bhatt, R.S., **Hock, A.,** White, H., Jubran, R., & Heck, A., (2017). *The development of structural and functional knowledge about bodies in infancy.* The Society for Research in Child Development, Austin, TX. April 5-7, 2017 (Paper-Symposium title: New Directions in the Study of Body Representations in Early Development).

Hock, A., Jubran, R., White, H., & Bhatt, R.S. (2016). *Configural face processing in newborn infants.* The International Congress on Infant Studies, New Orleans, LA. May 26-28, 2016 (poster presentation).

Jubran, R., **Hock, A.,** White, H., Heck, A. & Bhatt, R.S. (2016). *Attraction of infants' attention by emotional body stimuli.* The International Congress on Infant Studies, New Orleans, LA. May 26-28, 2016 (poster presentation).

White, H., **Hock, A.,** Jubran, R., Heck, A. & Bhatt, R.S. (2016). *Categorical perception of species in infancy.* The International Congress on Infant Studies, New Orleans, LA. May 26-28, 2016 (poster presentation).

Hock, A., Jubran, R., White, H., & Bhatt, R.S. (2015). *Infants' attention to emotion in bodies.* The Society for Research in Child Development, Philadelphia, PA. March 19-21, 2015 (poster presentation).

Hock, A., White, H., Jubran, R., & Bhatt, R.S. (2015). *Development of body representation in infancy: Scanning of specific body regions of the different sexes.* The Society for Research in Child Development, Philadelphia, PA. March 19-21, 2015 (poster presentation).

Bhatt, R.S., Kangas, A., **Hock, A.** & Oberst, L. (2014). *Perceptual learning and face processing in infancy.* The International Congress on Infant Studies, Berlin, Germany. July 3-5, 2014 (Talk-Symposium title: Development of Face Processing in Infancy: Behavioral, Eye Tracking, and Neuroimaging Studies).

Hock, A., Oberst, L., & Bhatt, R.S. (2014). *Matching of facial and body emotion information in infancy.* The International Congress on Infant Studies, Berlin, Germany. July 3-5, 2014 (poster presentation).

Hock, A., Oberst, L., & Bhatt, R.S. (2014). *The development of holistic processing of non-human animal stimuli.* The International Congress on Infant Studies, Berlin, Germany. July 3-5, 2014 (poster presentation).

Hock, A., & Bhatt, R.S. (2014). *The development of face processing expertise in newborn infants.* The Children at Risk Conference, Lexington, Kentucky. April 17-18, 2014 (poster presentation).

Kangas, A., **Hock, A.,** Zieber, N., & Bhatt, R.S. (2013). *What goes with what? Infants' knowledge of gender in faces and bodies.* The Society for Research in Child Development: Seattle, WA. April 18-20, 2013 (poster presentation).

Hock, A., Zieber, N., Oberst, L., Kangas, A., & Bhatt, R.S. (2013). *The development of body knowledge in infancy: Sensitivity to the waist-to-hip ratio.* The Society for Research in Child Development: Seattle, WA. April 18-20, 2013 (poster presentation).

Hock, A., Kangas, A., Zieber, N., & Bhatt, R.S. (2013). *The whole picture: Body posture recognition in infancy.* The Society for Research in Child Development: Seattle, WA. April 18-20, 2013 (poster presentation).

Grants and Research Support

Hock, A. (2016, December). *Processing of spatial information in social and non-social stimuli by opioid-exposed and non-exposed newborns*. APA Dissertation Research Award.

Hock, A. (2015, October). *The development of visual memory capacity in healthy and opioid-exposed infants*. National Institute on Drug Abuse R36 Grant. Impact score of 43 but not funded.

Hock, A. (2015, October). *Early cognition in opioid-exposed infants.* Center for Drug Abuse Research Translation at the University of Kentucky. Funded.

Teaching Experience

Spring 2016	Instructor, Application of Statistics in Psychology Lecture and Lab
Fall 2015	TA, Processes of Psychology Development Lab under Dr. Ramesh Bhatt
Fall 2014	TA, Application of Statistics in Psychology Lab under Dr. Peggy Keller

Fall 2013	TA, Application of Statistics in Psychology Lab under Dr. Robert Lorch
Fall 2012	TA, Experimental Psychology Lab under Dr. Andrea Friedrich
Fall 2011	TA, Introduction to Psychology Lab under Dr. Ray Archer