The Impact of Dark-Rearing on Auditory Enhancement of Visual Detection and Localization

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ABSTRACT

Multisensory neurons in the superior colliculus develop their ability to integrate cross-modal cues over time. Physiological studies have been conducted on cats looking at the consequences of removing early sensory experiences on the maturation of these neurons. These studies show that multisensory neurons fail to develop their integrative capabilities. The behavioral consequences of this lack of integrative capabilities have not been examined. To observe these consequences, animals were raised in the absence of visual cues and then tested in a detection and localization paradigm. These animals were found to not exceed statistical facilitation in the cross-modal condition. This suggests that the physiological consequences predict the responses to these stimuli in awake behaving animals.

Introduction

The superior colliculus is a midbrain structure whose function is the control of orientation behavior. It integrates information across multiple modalities which results in a response that is significantly different from the components' response. This ability is not exhibited at birth; rather it emerges due to cross-modal experiences during the first few months of life (Wallace & Stein, 1997).

Physiological studies have been conducted using different rearing conditions to determine the importance of experiences with concordant cross-modal cues in the development of the multisensory integration ability (Yu, Rowland, & Stein, 2010; Xu, Yu, Rowland, Stanford, & Stein, 2012; Xu, Yu, Rowland, Stanford, & Stein, 2014). These rearing conditions result in SC multisensory neurons that can process visual and auditory signals, but are unable to integrate this information together to yield multisensory enhancement (Yu, Rowland, & Stein, 2010; Xu, Yu, Rowland, Stanford, & Stein, 2014). The responses of the multisensory neurons in these animals are no different than the responses to the best modality-specific cue. One question that has not been answered is what are the behavioral consequences of not developing multisensory integration?

To answer this question, dark-reared animals were trained and tested in a detection and localization paradigm using visual and auditory stimuli. Based on the physiological results, the behavioral outcomes might show that the cross-modal condition is no different than the unisensory conditions. However, because the SC also contains modality-specific neurons, I hypothesize that the animal will perform significantly better on the cross-modal cues than the modality-specific cues. This is because the cross-modal cue would activate

both the visual and auditory unisensory neurons in the SC and this activation increases the information for the animal to use to make the correct decision in the task.

This study aims to answer the question of the behavioral effects of dark-rearing cats thereby adding a behavioral study to the electrophysiological work that has been conducted.

Multisensory Integration

We receive sensory information in many different forms and each sense transduces a different form of energy. Further, we must be able to process this information and make use of it in the most effective way. While there are primary sensory areas in the brain for each of the sensory modalities, there are also associated regions that house multisensory neurons. Researchers have found neurons that can respond to all of the combinations of visual, auditory, and tactile information, including tri-sensory neurons that are able to respond to all three (Stein & Meredith, 1993; Stein & Stanford, 2008).

Integration can lead to an enhancement, depression or no change in the resultant response (Stein & Meredith, 1993; Jiang & Stein, 2003; Stein B. , Stanford, Ramachandran, Perrault, & Rowland, 2009). Multisensory enhancement is defined as when the response to a cross-modal stimulus is significantly greater than the response of the component stimuli (Stein, Stanford, & Rowland, 2014). Enhancement may yield responses that are the same, less than or greater than the sum of the responses to the individual component stimuli (Stein B. , Stanford, Ramachandran, Perrault, & Rowland, 2009). Multisensory integration is examined in physiological studies by comparing the number of impulses evoked by the most effective modality-specific stimulus to the impulses evoked by the cross-modal stimulus (Figure 1) (Meredith & Stein, 1983; Meredith & Stein, 1986; Wallace & Stein,

1997). This integration ability has been found in many different areas such as the primary visual cortex thalamus, inferior colliculus and most notably the superior colliculus (Stein & Meredith, 1993).

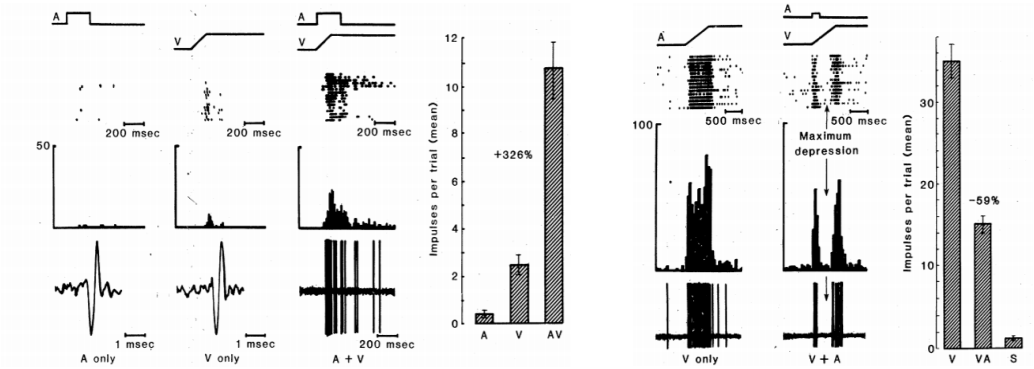

Figure 1: Electrophysiological data showing enhancement and depression of neuronal response. Response enhancement (left) has as a super additive effect where the multisensory response is greater than the sum of the individual components. Response depression (right). From (Meredith & Stein, 1983).

The Superior Colliculus

The multisensory properties of the superior colliculus (SC) have been investigated in multiple species. It is a paired structure of the mammalian midbrain made up of three different layers: superficial, intermediate and deep (Stein & Meredith, 1993; Haines, 2013). The neurons in the superficial layer are purely visual and receive direct input from the retina (Boehnke & Munoz, 2008; Sterling, 1973), visual cortical areas (17, 18, 19) and frontal eye fields (Huerta & Harting, 1984; Harting, Updyke, & van Lieshout, 1992). The neurons of the intermediate and deep layers are the primary sites of multisensory convergence and receive inputs from a variety of subcortical and cortical areas, e.g., anterior ectosylvian sulcus (AES) and rostrolateral sulcus (rLS) (Wallace, Meredith, & Stein, 1993).

The AES is very important for the multisensory properties of the intermediate and deep layers of the SC (Harting, Updyke, & van Lieshout, 1992). It is divided into three sub-regions: the anterior ectosylvian visual area (AEV) (Olson & Graybiel, 1987; Jiang, Lepore, Ptito, & Guillemot, 1994), the auditory field of the AES (FAES) (Clarey & Irvine, 1986; Meredith & Clemo, 1989; Jiang, Lepore, Ptito, & Guillemot, 1994) and somatosensory area IV (SIV) (Clemo & Stein, 1982; 1983; 1984), each of which are primarily modality-specific. These three areas of the AES project modality-specific information to the deep layers of the SC and create a map of space that align on the SC (Figure 2). Additionally, these sensory maps overlap with a motor map which allows for the SC to be very efficient in sensorimotor transduction (Stein & Stanford, 2008).

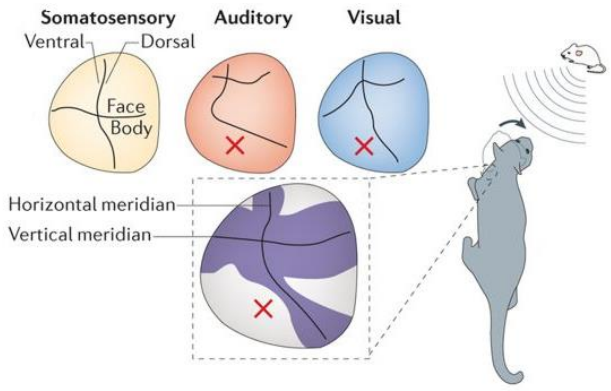

Figure 2: The Anterior Ectosylvian Sulcus mapping on the SC. The auditory, visual and somatosensory inputs create a map of space that align on the SC. This results in multisensory neurons that can respond to more than one sensory modality when presented in the same location in space. From Stein et al 2008.

Most of the neurons in the deep layers send efferent neurons to motor regions of the brainstem and spinal cord (Wurtz & Goldberg, 1972). These neurons of the SC mediate the animal's ability to detect and localize external events and orient to them, thus they need to synapse on the motor neurons that control these movements (Burnett, Stein, Chaponis,

& Wallace, 2004). A few movements that the SC mediates are: eye movements (Schiller & Stryker, 1972; Straschill & Hoffmann, 1970; Wurtz & Goldberg, 1972), eye and head movements (Chen & Walton, 2005; 2007; Gandhi & Katnani, 2011), pinnae and whisker movements (Cowie & Robinson, 1994; Hemelt & Keller, 2008; McHaffie & Stein, 1982; Stein & Clamann, 1981) and fixation control (Munoz & Guitton, 1989; 1991; Munoz & Wurtz, 1993).

Principles of Multisensory Integration

Three general principles of multisensory integration in the neurons of the adult cat's SC have been determined over many years of research. Two of the principles involve spatial and temporal cues and the final one involves the effectiveness of the cue (Meredith, Nemitz, & Stein, 1987; Kadunce, Vaughan, Wallace, & Stein, 2001).

The first two principles state that there is typically an enhancement in the response of multisensory neurons if cross-modal cues are in the same or close spatial and temporal receptive fields (Figure 3; top) (Kadunce, Vaughan, Wallace, & Stein, 2001; Meredith, Nemitz, & Stein, 1987). Conversely, cues that are disparate spatially and/or temporally do not interact at all or result in a depression of the response (Figure 3; bottom) (Kadunce, Vaughan, Wallace, & Stein, 2001; Meredith, Nemitz, & Stein, 1987).

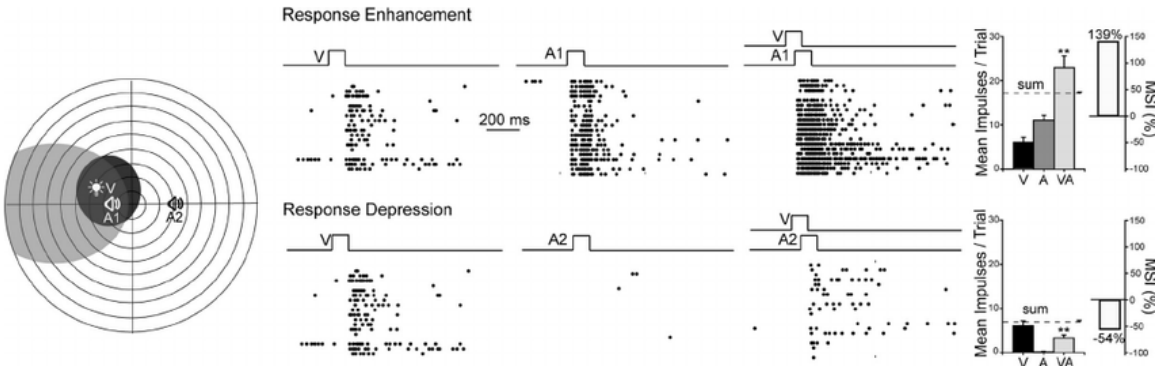

Figure 3: First and Second Principle of Multisensory Integration. On top shows the first principle of multisensory integration in effect. When the visual and auditory cue were spatially and temporally concordant, enhancement was seen in the cross-modal condition. On the bottom the second principle is shown. Here, when the visual and auditory conditions are spatially disparate there is a depression in the response. From (Xu, Yu, Rowland, Stanford, & Stein, 2012).

The final principle, inverse effectiveness, depends on the strength of the individual cues being combined (Figure 4). Modality-specific cues that evoke a strong response results in a smaller enhancement with the cross-modal cue. However, if the modality-specific cue evokes a weak response, the proportional enhancement of the cross-modal stimulus is substantially greater (Meredith & Stein, 1983).

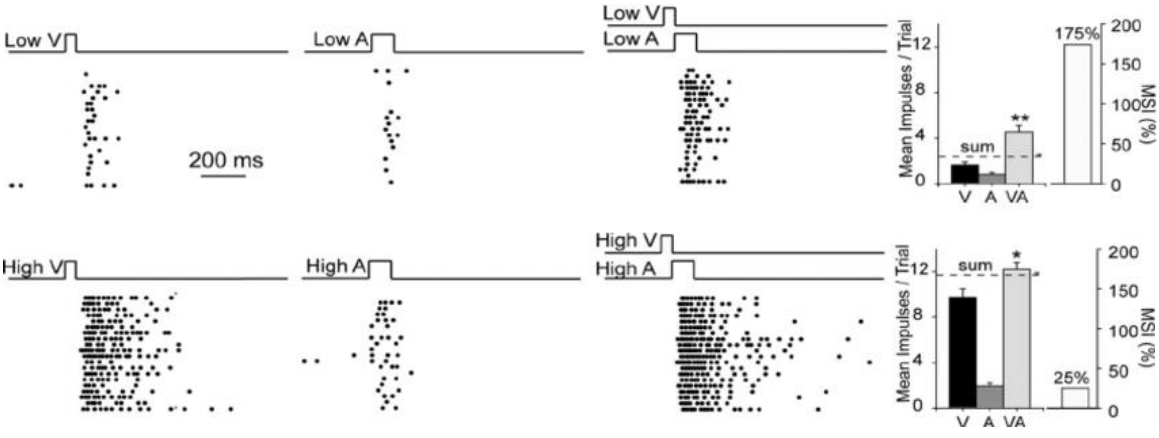

Figure 4: Inverse Effectiveness. The third principle of multisensory integration is shown above. As the stimulus intensity increased, the unisensory and multisensory responses also increased. Because the strength of the unisensory response also increased, the enhancement over

the modality-specific condition decreased. Adapted from (Xu, Yu, Rowland, Stanford, & Stein, 2012).

These principles have been tested over many years and many different experiments and have proven to be consistent across all experiments. Further, the principles themselves are consistent with the idea that multisensory integration improves the ability to localize and detect events in space and in time (Meredith & Stein, 1986; Kadunce, Vaughan, Wallace, Benedek, & Stein, 1997; Pluta, Rowland, Stanford, & Stein, 2011).

Development of Multisensory Integration

It is important to note that in newborn cats, the SC has no functional multisensory neurons that are capable of integration. Following birth, somatosensory neurons are the only sensory-responsive neurons (Stein, Labos, & Kruger, 1973; Wallace & Stein, 1997). The eyes and ears remain closed for many days after birth. After the ear canals open, auditory responsive neurons emerge in the SC and visual neurons emerge at around 20 dpn, (Figure 5) (Wallace & Stein, 1997; Jiang, Stein, & McHaffie, 2009). As the multisensory neurons emerge, they initially respond weakly to sensory stimuli, have long latencies, and poorly developed response discernment (Wallace & Stein, 1997). However, exposure to cross-modal experiences initiates the development of these neurons (Wallace & Stein, 1997; Yu, Rowland, & Stein, 2010).

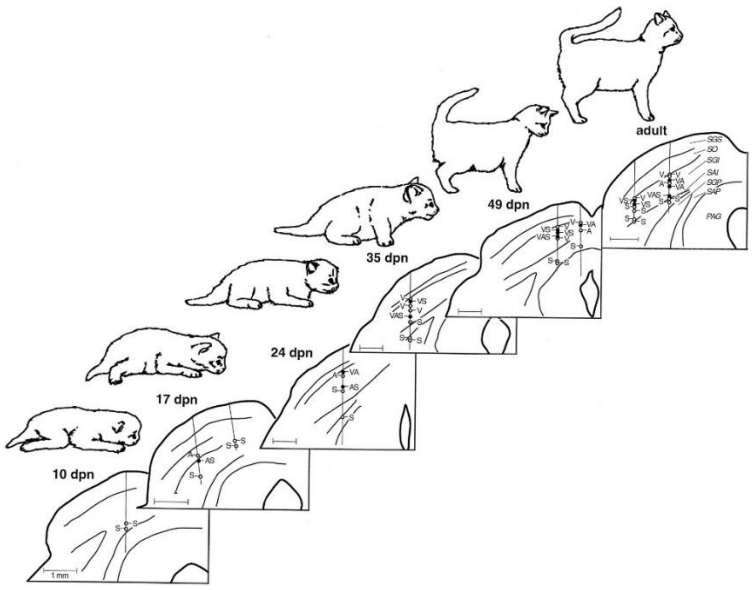

Figure 5: Sensory-responsive neurons during development. Histological reconstructions of coronal sections through the SC are shown. Six different developmental stages displaying the unimodal and multisensory neurons in the SC. First to develop are somatosensory only neurons and then auditory unimodal and auditory-somatosensory are shown at 17 days postnatal. At 24 days postnatal visual-auditory neurons are developed next with and finally we see an emergence of trisensory neurons that integrate visual, auditory and somatosensory. Open circles are unimodal neurons and closed circles are multisensory neurons. From (Wallace & Stein, 1997).

The receptive fields of each modality are large and then gradually get smaller as the cats mature (Wallace & Stein, 1997). The contraction of the receptive fields is due to exposure to unisensory information, which improves the reliability of spatial representations and gives higher alignment among each of the sensory modalities (Figure 6). Additionally, this contraction is typically accompanied by an increase in to the number of neurons that are capable of multisensory integration (Wallace & Stein, 1997).

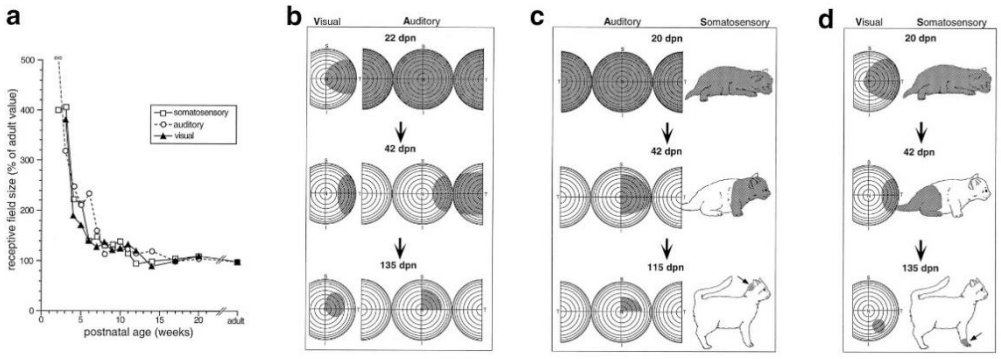

Figure 6: The receptive fields of multisensory neurons decline during development. A) Receptive field size is plotted versus postnatal age of kittens. B) Receptive fields of visual–auditory neurons shown at three different postnatal days. Plotted onto representations of visual and auditory space (shading). C) Receptive fields of auditory-somatosensory neurons shown at three different postnatal days. D) Receptive fields of visual–somatosensory neurons shown at three different postnatal days. Plotted onto representations of visual and somatosensory space (shading). From (Wallace & Stein, 1997).

Impact of Dark-Rearing on Multisensory Integration

Studies have examined the importance of cross-modal experiences during development and how manipulation of these experiences affects the maturation of the neurons in the SC of cats, monkeys and humans (Carlson, Pertovaara, & Tanila, 1987; Carriere, et al., 2007; Putzar, Goerendt, Lange, Rösler, & Röder, 2007; Royal, Krueger, Fister, & Wallace, 2010). Depriving animals of visual-nonvisual interactions (dark-rearing) by raising them in the dark is one way to study the importance of cross-modal experiences during development (Wallace, Perrault, Hairston, & Stein, 2004; Xu, Yu, Rowland, Stanford, & Stein, 2012; Yu, Rowland, & Stein, 2010; Yu L. , Xu, Rowland, & Stein, 2013).

Dark-rearing has been shown to alter the proportion of sensory-responsive neurons in the SC and AES (Carriere, et al., 2007; Wallace, Perrault, Hairston, & Stein, 2004). Dark-rearing also increases the probability of multisensory AES neurons showing response

depressions to spatiotemporal coincident stimuli (Carriere, et al., 2007). The shrinking of the receptive fields of the multisensory neurons in the SC that we see in normal development is not seen in these compromised animals. Dark-rearing also yields a significantly lower incidence of visual-nonvisual neurons capable of multisensory integration (Figure 7) (Yu L. , Xu, Rowland, & Stein, 2013; Xu, Yu, Stanford, Rowland, & Stein, 2015).

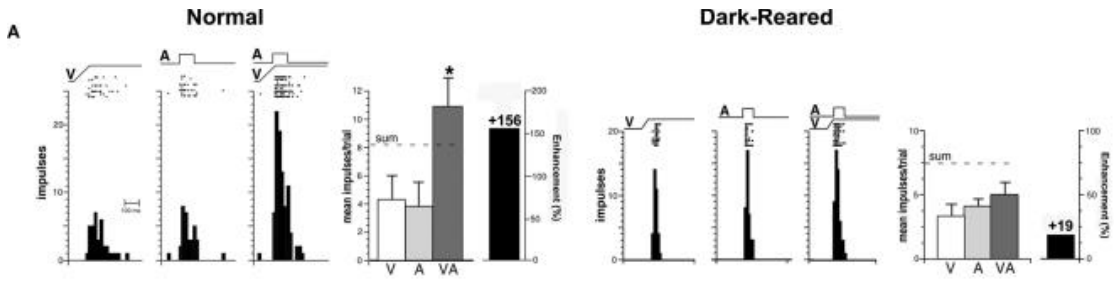

Figure 7: Electrophysiology of dark-reared animals in the absence of cross-modal experience. Normal raster shown on the left and dark-reared animals raster shown on right. Impulses per trial show that dark-reared animals do not exhibit enhancement with visual and auditory cross-modal cues, while normal animals show enhancement. From (Wallace, Perrault, Hairston, & Stein, 2004).

Experiments have also been conducted with dark-reared animals that were exposed to either visual–auditory stimuli that were in spatiotemporal concordance or modality-specific stimuli that were presented randomly in space and time during development (Figure 8) (Xu, Yu, Rowland, Stanford, & Stein, 2012). These experiments showed that the animals that were exposed to cross-modal stimuli developed normal multisensory integration capabilities while the animals exposed to random modality-specific cues did not (Xu, Yu, Rowland, Stanford, & Stein, 2012).

Multisensory integration can be developed in dark-reared adult animals. These integrative capabilities have been acquired through exposure to repeated presentations of

cross-modal stimuli within their own receptive fields (Yu, Rowland, & Stein, 2010). Further, once this ability has been acquired at one receptive field location, it is generalized to all other locations (Yu, Rowland, & Stein, 2010).

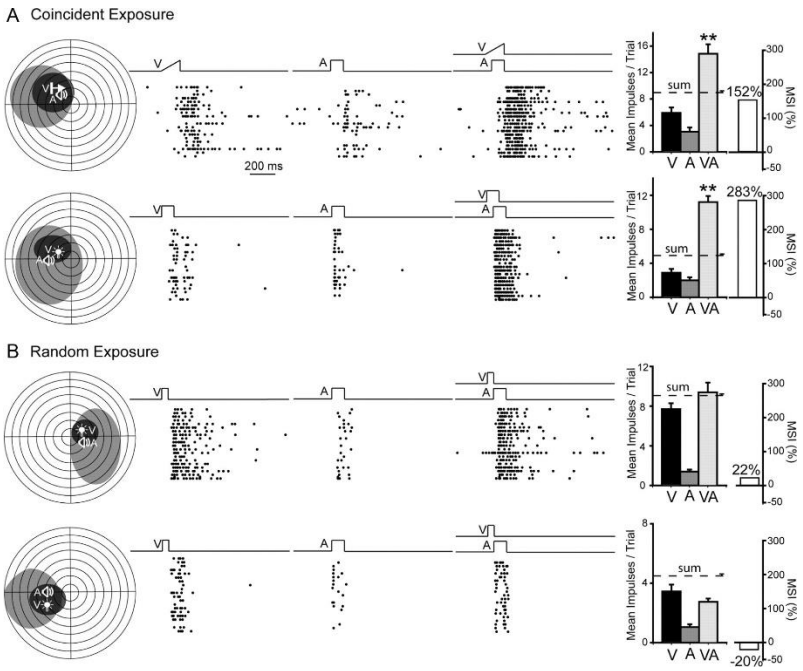

Figure 8: Multisensory integration develops after cross-modal exposure, but not after random exposure. A) Coincident exposure produced the normal expression of multisensory integration and multisensory enhancement. B) Random modality-specific exposure failed to produce multisensory integration capabilities. Error bars represent the SEM. Receptive fields are contralateral to the SC of the recorded neurons. From (Xu, Yu, Rowland, Stanford, & Stein, 2012)

There have also been deprivation studies in humans (Putzar, Goerendt, Lange, Rösler, & Röder, 2007; Putzar, Hötting, & Röder, 2010; 2012). Adults who were born with dense binocular cataracts served as the model for studying the role of early visual experience in sensory development. Individuals went 5-24 months without visual experience before being treated for binocular cataracts (Putzar, Goerendt, Lange, Rösler, & Röder, 2007; Putzar, Hötting, & Röder, 2010; 2012; Heering, Pelland, Lewis, Maurer, & Collignon, 2016). Studies conducted when they were adults showed that they

performed significantly worse in audio-visual speech perception tasks than normal patients due to their multisensory integration capabilities being compromised (Putzar, Goerendt, Lange, Rösler, & Röder, 2007). A recent study showed that these patients performed similar to normal patients in simple detection tasks, beating what a race model (described below) would predict (Heering, Pelland, Lewis, Maurer, & Collignon, 2016).

Evaluating Multisensory Integration in Behavior

The behavioral outcomes of multisensory processing in the SC have been studied using a variety of different tests such as reaction time, localization and detection, etc. (Miller J. , 1982; Stein, Meredith, Huneycutt, & McDade, 1989; Gingras, Rowland, & Stein, 2009). Colonius and Diederich give an overview of many of the models that have been used to describe multisensory integration in different behavioral tasks (Colonius & Diederich, 2017). It is important to note that because it is the behavior that is being measured and not the neuronal responses, integration cannot be concluded by simply comparing the cross-modal response to the best unisensory response. Instead, a separate activation model predicting the response of no interaction between modalities is necessary as a comparison for cross-modal responses in order to make the conclusion that integration is occurring.

A separate activation model has been described for reaction time studies (Miller J. , 1982). The separate activation model states that "signals on different channels produce separate activations, each of which builds to the level at which it can produce a response" (Miller J. , 1982). Meaning that on cross-modal trials, the response is controlled by the detection of a signal on only one of the channels. Separate activation models are typically called race models due to the response being determined by the cue that is processed faster

or the "winner of the race" (Miller J. , 1982). The model predicts a "statistical facilitation" effect where the cross-modal predicted response is faster than either of the modality specific responses (Miller J. , 1982; Raab, 1962).

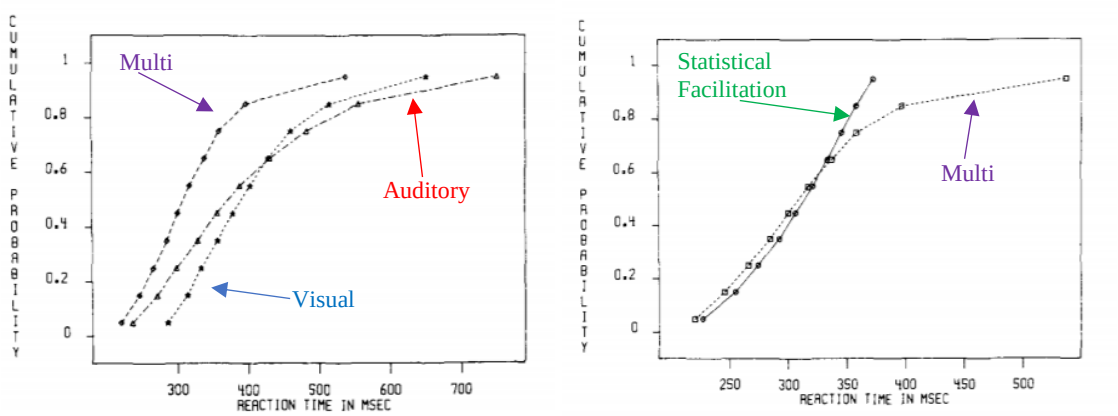

Figure 9: Race Model for Reaction Time. Experimental results measuring reaction times using visual and auditory signals are shown above. The responses were determined by pressing a key on the keyboard of the computer with the right index finger. Left: Multisensory condition is statistically different than either of the unisensory conditions. Right: Separate-activation model is plotted with the multisensory responses. The separate-activation models require that the dash curve be everywhere to the right of the solid curve. From (Miller J. , 1982).

A separate activation model has not been adapted for a detection and localization task. Instead, cross-modal enhancements are compared to within-modal (visual-visual or auditory-auditory) enhancements to show significant differences in multisensory integration (Gingras, Rowland, & Stein, 2009).

Multisensory Integration: Summary

To conclude, the SC is a midbrain structure that receives sensory inputs from many different areas. Its primary function is localization, detection and orientation of salient events. Important inputs to the SC are projections from the rostrolateral suprasylvian and anterior ectosylvian sulcus which projects auditory, visual and somatosensory inputs.

These ascending projections from the AES to the SC form sensory maps that overlap and align with each other. Additionally, these projections, along with cross-modal experiences, are critical for the development of multisensory integration. Multisensory enhancement, which is when the response of cross-modal stimulus is greater than the response of the modality specific stimuli, has been shown both physiologically and behaviorally. This ability is not present at birth, rather it emerges due to cross-modal experiences during the first few months of life (Wallace & Stein, 1997). Manipulation of cross-modal experiences can lead to defects in multisensory processing, however, the behavioral outcomes of these defects have yet to be experimentally shown.

Methods

All procedures were conducted in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication) and an approved Institutional Animal Care and Use Committee protocol at Wake Forest University School of Medicine, an Association for Assessment and Accreditation of Laboratory Animal Care-accredited institution. Kittens were deprived of any visual or cross-modal experiences by being placed in a light tight (dark) room within a week of birth.

Behavioral Apparatus:

All animals were trained in a windowless room on a black perimetry apparatus that was 90cm in diameter. Along the walls of the apparatus were complexes each of which contained two speakers and three LEDs below. LEDs were 4cm apart from each other and were 4cm below the two speakers. The complexes were separated by 15° ranging from -105° to 105° (Figure 10). Only one of the LEDs (left most) and speakers (left) were used

during the behavioral training and testing. A specially designed software was used to allow the experimenter to trigger the stimuli, which consisted of a 50ms light flash or broadband noise burst during the task. An infrared lamp and night vision goggles were used to help the experimenter carry out the training and testing.

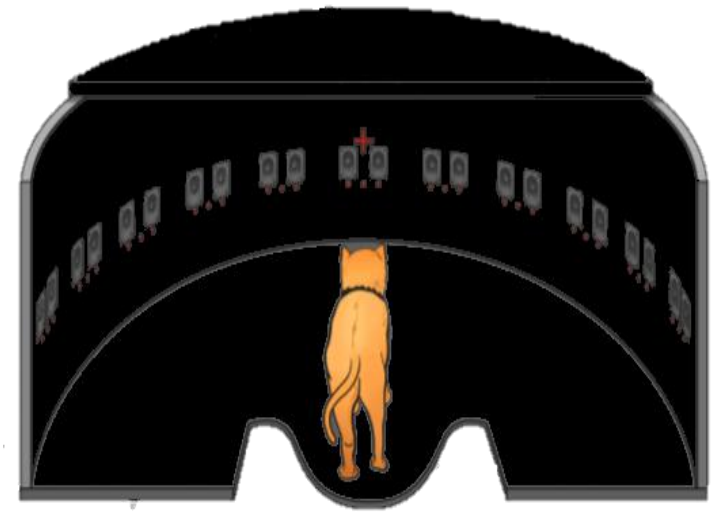

Figure 10: Perimetry Device. Apparatus contains LEDs and speakers at 15° increments ranging from -105° to 105° with a central fixation point at 0°. LEDs and speakers were grouped such that there were three LEDs and two speakers at each location.

Behavioral Training:

Animals were trained in a localization task to approach a stationary visual cue and an auditory cue (white noise burst). Training was carried out under two conditions: no light, dim light, normal light. To begin, animals were trained to stand at the center of the apparatus (Figure 10) and fixate directly ahead at 0°. A foot pedal was used to trigger cue presentations. There were 3 possible stimuli that could be presented to the animal in any given trial: auditory, visual, or catch where no stimuli were given. For the catch trial, the animals were trained to stay fixated at 0° to receive the food reward. If the animal did not

approach the target the trial was scored as a "no-go." When an auditory or visual stimulus was present in a trial, the animal had to orient toward and approach the correct location to receive the food reward. The animals were trained to approach seven locations: six locations on the left and right (-45° to +45°) and the center location (0°). This training continued until the accuracy for catch trials and the correct approach at each location reached 80%.

Behavioral Testing:

Intensities of the unisensory conditions (visual or auditory) were reduced so that the correct response rate at each location was ~30-40%. This was defined by a 30-40% correct approach behavior to each location across at least 20 trials. Animals were trained to satiety each day which resulted in 125-200 trials per day and 5 days per week. A multisensory condition (auditory-visual) was added, increasing the possible conditions to 4 across each location. The auditory and visual stimuli in the multisensory condition were spatially and temporally equivalent. The four stimulus conditions were randomly interleaved:

1) a single auditory stimulus (A)

2) a single visual stimulus (V)

3) a spatiotemporally coincident visual–auditory stimulus pair (VA)

4) a catch trial

A food reward was given for orientation and approach to each target stimulus or maintaining fixation and no movement during a catch trial. Due to the animals running to satiety each day using random trial selection, there were an unequal number of trials/day/

location. All cue combinations were tested for at least 55 trials per location; however, there were some locations that exceeded this number of trials.

Data Analysis:

Each trial was scored by the researcher as correct, incorrect or No-Go and then grouped according to location (±45°, ±30°, ±15°, 0°) and stimulus type (visual, auditory, multisensory, or catch). A χ^2 test for significant differences was used to determine the differences between categories. This test was used to compare the localization performance of the best modality-specific condition to the multisensory condition (MC). The multisensory enhancement (MSE) between the best unisensory condition (BUC) and multisensory condition was calculated using Eq. 1.

$$MSE(\%) = \frac{MC - BUC}{BUC} \times 10 \quad (1)$$

The multisensory performance was then compared over a statistical facilitation model to examine the extent of integration of the auditory and visual signals described below (**Error! Reference source not found.**).

Statistical Facilitation Model

A statistical facilitation model was used to examine the extent to which the auditory and visual signals were integrated (Figure 11). This model utilizes the auditory and visual only performances to determine a multisensory predicted response. First, the auditory and visual responses are separated by target location and pooled together. For example, all of the responses the animal made for auditory only trials at 0° were pooled together with the responses the animal made for visual only trials at 0°. An auditory and visual response is then randomly sampled from this pool of data and compared to one another. The response that is more accurate determines the cross-modal predicted response. These steps were

repeated for 10,000 trials for each location and then the average correct response was calculated. The statistical facilitation response was compared to the experimental multisensory response using Eq.1. Finally, a χ^2 test for significant differences was used to determine if the experimental multisensory response was significantly different from the modeled predicted response.

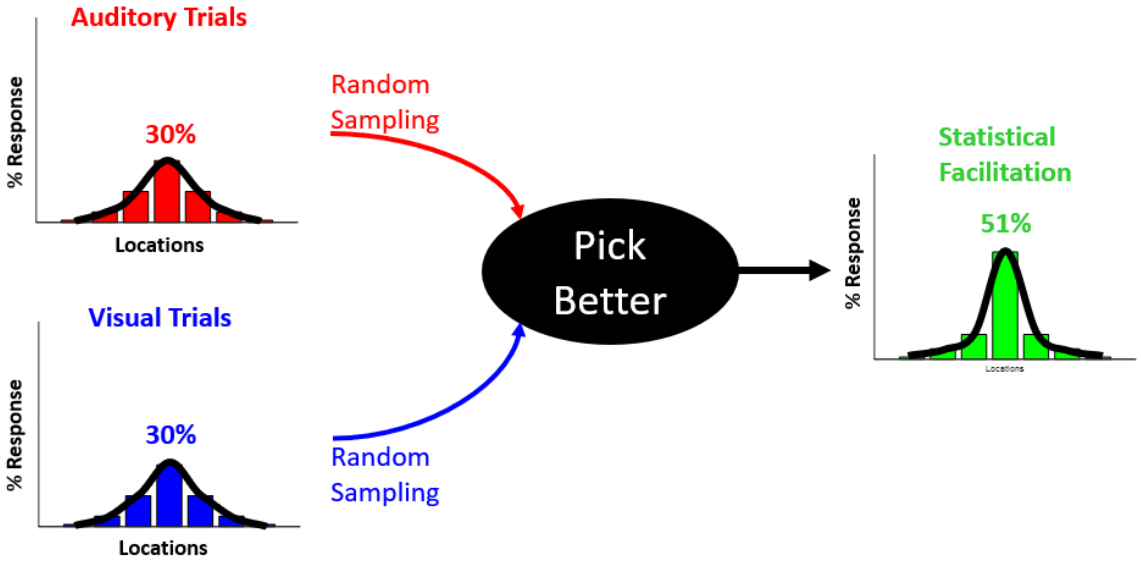

Figure 11: Statistical facilitation prediction for no interaction. This model gives a predicted multisensory response if there was no interaction between the cues. The auditory and visual only trials were pooled by location. Auditory and visual responses were then randomly sampled from the pool and compared to each other. The response that was more accurate determine the predicted response of the model.

Results: Behavior Analysis

Normal cat (n=4) results are taken from data previously acquired by Gingras, Rowland and Stein (2009). All animals learned to localize and approach the targets at perimetric positions outlined above. Performance for each stimulus condition during testing was consistent across all animals within normal rearing condition. The data were pooled across animals for analysis.

Normal Animals: Data were collapsed across all four animals to generate an average response (Figure 12A). Average correct approach response for auditory and visual only conditions were 27 and 25%, respectively. The cross-modal condition of a spatial and temporal concordant cue showed significant enhancement above all locations (χ^2 test, $p<0.01$). The average enhancement of the cross-modal condition over the best unisensory condition was 136% (Figure 12A) and ranged from 94 to 168% across locations (Figure 12B).

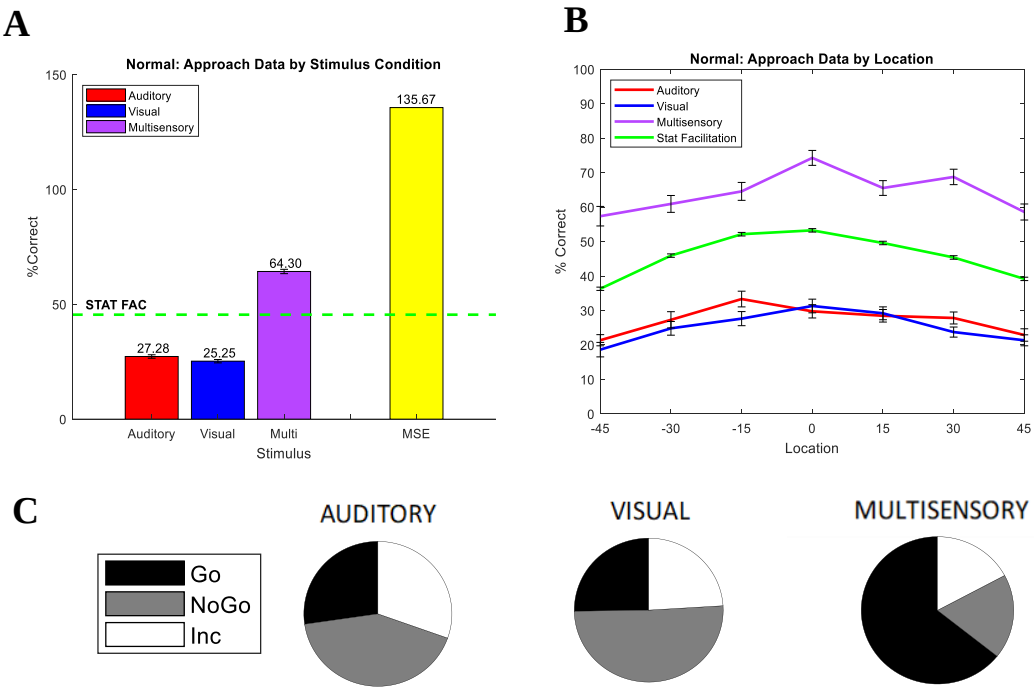

Figure 12: Behavioral results for Normal animals (n=4). Multisensory enhancement seen over statistical facilitation (χ^2 test $p<0.001$). A) Means and standard errors are plotted for each condition. Labels above each bar represent the average for each stimulus type. Auditory approach rate was no different than the visual approach rate (χ^2 test $p=0.1346$). MSE shown is cross-modal approach over the best unisensory approach. B) Means and standard errors are plotted for each location and each condition. C) The pie charts show the performance for the auditory, visual and multisensory conditions. "Go" represents the total trials of correct approaches. "NoGo" represents trials where the animal did not move. "Inc" represents trials where the animal moved but approached the wrong location.

Dark Animals: Training data for two dark-reared animals are shown in Figure 13. Animals were trained in the same conditions for dark-rearing but tested by different experimenters. All data from Cat 1 were collected by Zhengyang Wang and data from Cat 2 were collected by Scott Smyre. Training for Cat 1 took one month to learn the task while training for cat 2 took almost four months.

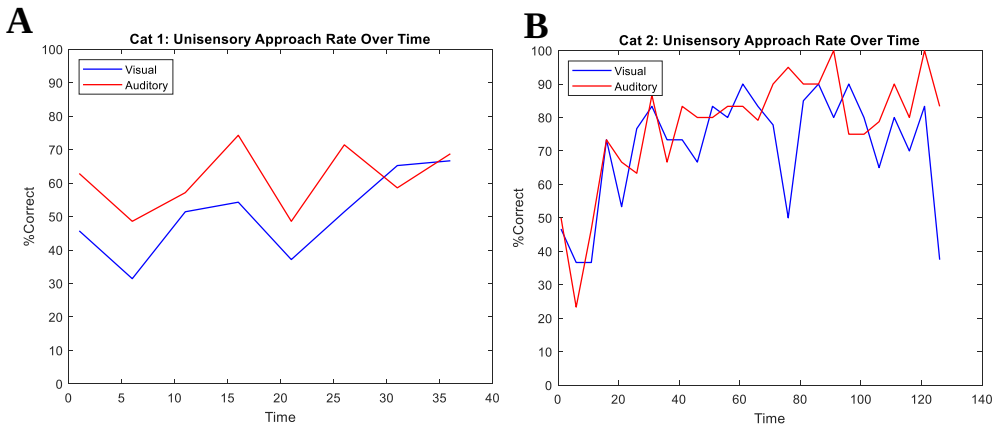

Figure 13:Training Data for Dark-Reared Animals. Approach rate for modality-specific cues are shown. A) Animal was trained using cues with 200ms duration (not shown) and then the duration was lowered to 50ms. B) Animal was trained using 50ms cue duration for all training trials. Note the difference in training time for Cat 1 and Cat 2.

Dark-reared Cat 1: The average response for the auditory and visual only stimuli were 25% and 18%, respectively, and were significantly different (χ^2 test, p=0.02). The approach to the cross-modal condition did not show significant enhancement above the best unisensory condition (χ^2 test, p=0.0771). Further, the cross-modal approach was significantly lower than what statistical facilitation predicts (χ^2 test, p<0.001). The average enhancement of the cross-modal condition was 20% over the best unisensory condition (Figure 14A) and had a range of -10% to 64% across locations (Figure 14B).

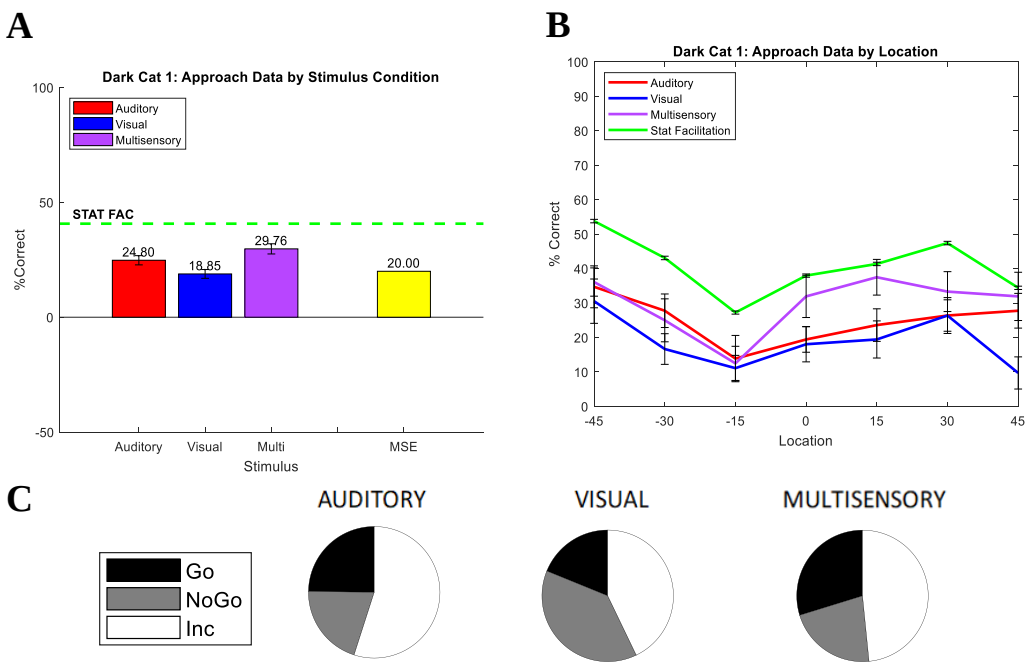

Figure 14: Behavioral results for Dark-reared animal Cat 1. Cross-modal approach rate is significantly lower than statistical facilitation (χ^2 test $p<0.001$). A) Means and standard errors are plotted for each condition. Labels above each bar represent the mean approach rate for each stimulus type. Auditory approach rate was significantly better than visual approach rate (χ^2 test $p=0.0222$). MSE shown is cross-modal approach over the best unisensory approach. B) Means and standard errors are plotted for each location. C) The pie charts show performance for the auditory, visual and multisensory conditions across all trials. "Go" represents the total trials of correct approaches. "NoGo" represents trials where the animal did not move. "Inc" represents trials where the animal moved but approached the wrong location.

Dark-reared Cat 2: The average correct approach response for the auditory and visual only stimuli were 37% and 36%, respectively, and were not significantly different (χ^2 test, $p=0.962$). The approach to the cross-modal condition showed significant enhancement above the best unisensory condition (χ^2 test, $p<0.001$). But, the cross-modal approach was no different than statistical facilitation (χ^2 test, $p=0.895$). The average enhancement of the cross-modal condition was 66.8% over the best unisensory response (Figure 15A) and had a range of 41% to 72% across locations (Figure 15B).

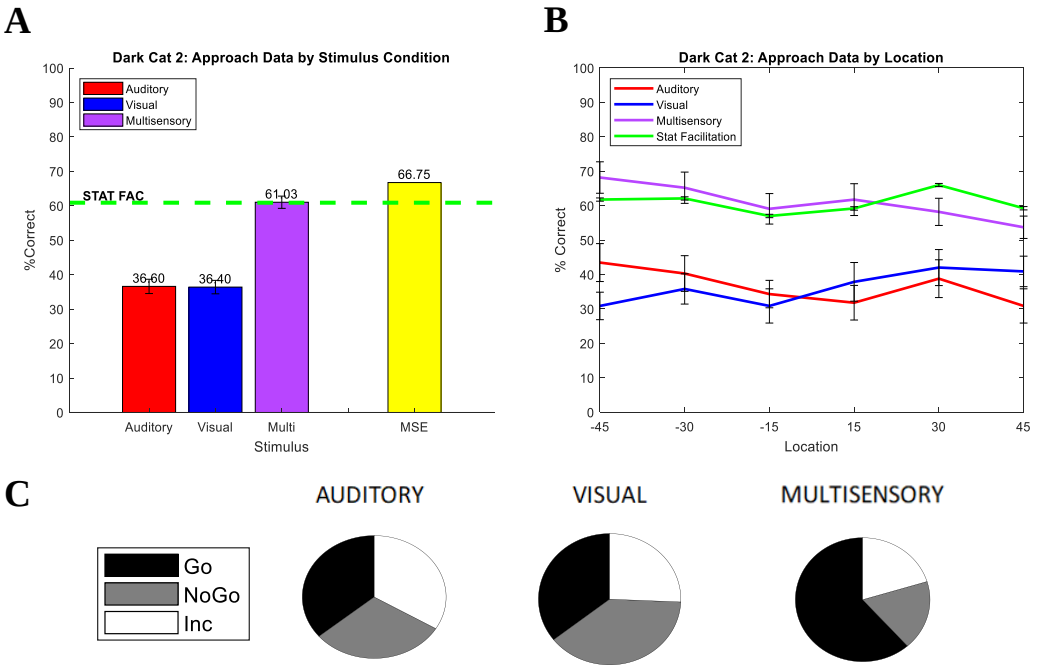

Figure 15: Behavioral results for dark-reared animal Cat 2. Cross-modal response is not significantly different than statistical facilitation (χ^2 test p=0.8950). A) Means and standard errors are plotted for each condition. Labels above each bar represent the mean approach rate for each stimulus type. Auditory approach rate was no different than the visual approach rate (χ^2 test p=0.9418). MSE shown is cross-modal approach over the best unisensory approach. B) Means and standard errors are plotted for each location. Enhancement exhibited across all locations over best unisensory response (χ^2 test p<0.001). C) The pie charts show performance for the auditory, visual and multisensory conditions across all trials. "Go" represents the total trials of correct approaches. "NoGo" represents trials where the animal did not move. "Inc" represents trials where the animal moved but approached the wrong location.

Discussion

Physiology studies have shown that depriving animals of modality-specific experiences of different sensory modalities results in the inability for SC neurons to develop normally (Yu, Rowland, & Stein, 2010; Xu, Yu, Rowland, Stanford, & Stein, 2014). The consequences of this deprivation are that the incidences of multisensory neurons in the SC that are capable of integration are significantly decreased. These neurons rarely show multisensory enhancement and the receptive fields across modalities are misaligned (Wallace, Perrault, Hairston, & Stein, 2004; Yu L. , Xu, Rowland, & Stein, 2013; Xu, Yu, Stanford, Rowland, & Stein, 2015). The data here suggests that the behavioral outcomes of dark-rearing matches the physiological deficits. Neither of the dark-reared animals beat statistical facilitation confirming that there are none or negligible interactions happening between the visual and auditory information.

Although neither of the animals beat statistical facilitation we see that the cross-modal responses are statistically different between animals. The major difference between the data collection of the two cats is the amount of training and thereby exposure to visual information that each received. Cat 1 received about 1 month of visual exposure whereas cat 2 received 4 months of visual exposure. Due to Cat 2 receiving more than 4x as much exposure to the visual information alone, it is possible that development of these multisensory neurons started to occur, and the receptive fields of these multisensory neurons began to shrink. This shrinking would improve reliability of spatial representations and give a higher alignment across the sensory modalities which could lead to the higher performance seen in Cat 2 and not Cat 1.

Traditionally, it was thought that the default state of multisensory processing was that there was no integration or interaction between the modality-specific signals (Stein, Stanford, & Rowland, 2014). As the animal matures, the state would transition to one where multisensory integration was occurring. However, a recent study suggests that the default mode of multisensory processing in the SC is competition, not non-integration (Yu L. C., Xu, Rowland, & Stein, 2019). This study revealed that increasing unisensory imbalances by varying the intensities of modality specific cues in dark-reared animals, resulted in the congruent cross-modal cues yielding response depression. Based on the results of this study, another possible explanation for the difference between animals is that the cross-modal cues were causing response depression in the multisensory neurons. The approach rate for the auditory cue was significantly higher than that of the visual cue in Cat 1 however there was no difference in the approach rate for visual and auditory only cues in Cat 2. Thus, based on the results in Yu et. al 2019, in Cat 2 there was no enhancement or depression in the response of the multisensory neurons, so we see behavior that is no different than statistical facilitation. However, in Cat 1, the depression in the response of the multisensory neurons could result in a behavioral response that is statistically lower than statistical facilitation. More animals would need to be trained and tested where the imbalance of these component cues varied to verify this conclusion.

Further physiological studies would need to be conducted on these animals to see if there is a difference in the size of the receptive fields of these animals and if the training had any consequences on the receptive field size. There was no change over time in the multisensory enhancement in both cats, so the testing conditions did not initiate any multisensory integration development. It has been shown that multisensory integration

capabilities can be developed in dark-reared adult animals (Yu, Rowland, & Stein, 2010). To do this, the dark-reared animals were presented with several spatiotemporal concordant cross-modal cues (). These animals could go through this training and be retested on this localization task to see if they display normal multisensory enhancement. This would confirm the physiological results and provide behavioral data these animals receive the same benefits as normal animals.

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Yu, L., Rowland, B. A., & Stein, B. E. (2010). Initiating the development of multisensory integration by manipulating sensory experience. *Journal of Neuroscience, 30*, 4904-4913.

Yu, L., Xu, J., Rowland, B. A., & Stein, B. E. (2013). Development of cortical influences on superior colliculus multisensory neurons: Effects of dark-rearing. *European Journal of Neuroscience, 37*, 1594-1604.

Yu, L., Xu, J., Rowland, B. A., & Stein, B. E. (2016). Multisensory plasticity in superior colliculus neurons is mediated by association cortex. Cerebral Cortex. *Cerebral Cortex, 3*, 1130-1137.

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CURRICULUM VITAE

EDUCATION

2017-2019 **M.S. Biomedical Sciences (Conc. in Neuroscience)**
Wake Forest University; Winston-Salem, NC
Advisor: Benjamin A. Rowland, Ph.D.
Thesis: "A Separate Activation Model for Behavioral Experiments"

2012-2016 **B.S. Biophysics, Honors; Minor: Chemistry**
Wake Forest University; Winston-Salem, NC

RESEARCH EXPERIENCE

2018-2019 Graduate Research Associate, Stein Lab
Wake Forest University; Winston-Salem, NC
PI: Barry Stein, Ph.D. and Benjamin Rowland, Ph.D.
- Research study is aimed at examining the multisensory integration capabilities of dark-reared animals using a behavioral localization task.
- Created a separate-activation model for localization task
- Studying the effects of multisensory integration on urgent decision-making
- Performed physiology experiments with cats

2016-2017 Laboratory Technician, Macosko Lab
Wake Forest University; Winston-Salem, NC
PI: Jed Macosko, Ph.D.
- Conducted a study assessing the effects of centrioles on mitotic division in cancer cells versus normal
- Handled all of the day to day cell care and performed experiments using the Atomic Force Microscope

2012-2016 Undergraduate Research Associate, Macosko Lab
Wake Forest University; Winston-Salem, NC
PI: Jed Macosko, Ph.D. and George Holzwarth, Ph.D
- Research study is aimed at examining the multisensory integration capabilities of dark-reared animals using a behavioral localization task.
- Assisted in studying the mechanical properties of cancer cells focusing on adhesion, migration, and response to the mechanical properties of its microenvironment

- Performed daily care for cells used in the study
- I conducted the experiments using sodium azide and 2-deoxy-glucose which reduces intracellular ATP and found that the breast cells were significantly softer than normal cells
- Examine different cross-linkers that would be used to create a matrix to study cancer cells. Created matrices and conducted assays to determine their mechanical properties

2012 High School Research Associate, Macosko Lab

Wake Forest University; Winston-Salem, NC
PI: Jed Macosko, Ph.D. and George Holzwarth, Ph.D

- Worked on a biology course for non-biology majors entitled BioBook
- Wrote multiple chapters for the biology course

PUBLICATIONS

Smelser, A.M., Gomez, M. M., **Smyre, S.**, Pashayan, M., Macosko, J.C. (2018). Stiffness-Tuned Matrices for Tumor Cell Studies. In S. Soker, & A. Skardal, Tumor Organoids (pp. 171-191). Winston-Salem: Springer International Publishing.

Smelser, A.M., Macosko, J.C., O'Dell, A.P., **Smyre, S.**, Bonin, K., Holzwarth, G., Mechanical properties of normal versus cancerous breast cells. Biomech Model Mechanobiology. 2015 November; 14(6): 1335–1347

PRESENTATIONS

INSTITUTION ASSOCIATED PRESENTATIONS

2019 Smyre, S., Stein, B.E., Rowland, B.A. Separate Activation Model for Behavior Experiments. Poster presentation at the *19th Annual Graduate Student and Postdoc Research Day, Wake Forest University*, Winston-Salem, NC. March 2019.

2018 Smyre, S., Stein, B.E., Rowland, B.A. Separate Activation Model for Behavior Experiments. Poster presentation at *Annual Student Research Day, Wake Forest University*, Winston-Salem, NC. November 2018.

2015 Smyre, S., Macosko, J. The synthesis and mechanical properties of 4-vinylbenzyl chloride cross-linked collagen. Poster presentation at *Undergraduate Student Research Day, Wake Forest University*, Winston-Salem, NC. October 2015.

LEADERSHIP AND OUTREACH

2018-Present Teaching Assistant
Department of Neurobiology & Anatomy
Wake Forest University; Winston-Salem, NC

- Helped develop and organize a curriculum for a 6-week neuroanatomy course for graduate students at Wake Forest University
- Helped facilitate weekly tutorial meetings answering student concerns and questions regarding the course
- Helped facilitate daily laboratory meetings for students
- Assisted in preparing brain models and slices to be used weekly in the laboratory

2018-Present Treasurer; Mentor
Brain Awareness Council; Winston-Salem, NC

- Update the financial budget
- Ensure that money used for events are documented and reported

2017-Present Mentor
S.Y.S.T.E.M; Winston-Salem, NC

- Serve as a mentor in a program which targets children living in single parent homes and growing up in poverty and coping with parental incarceration
- Meet monthly to design activities that will help to engage the students and push them to becoming the best they can be

2014-2016 President
Minority Association of Premedical Students; Winston-Salem, NC

- Minority Association of Pre-medical Students, or MAPS, represents the undergraduate and post-baccalaureate students of the Student National Medical Association (SNMA); helping to increase the number of minorities in the health field by providing events with current medical students, inviting speakers from medical schools and building connections with physicians
- I helped re-establish the chapter on the Undergraduate Campus of Wake Forest University
- Organized monthly meetings with the goal of coming up with events to help all pre-medical students on the undergraduate campus

SKILLS

Computer: Proficient with Matlab and R programming
Laboratory/Certifications: Proficient in Atomic Force Microscopy; American Association for Laboratory Animal Science Training