MULTISENSORY NETWORKS IN PRIMARY AND ASSOCIATION CORTICES IN CAT

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DEDICATION

TO ALL THE LITTLE GIRLS WHO WANTED TO BE PASTRY CHEFS WHEN THEY GREW UP ONLY TO DISCOVER THE JOYS OF SPECTRAL LINES OF THE ELEMENTS OF THE PERIODIC TABLE IN 7TH GRADE CHEMISTRY CLUB THAT SPARKED A LIFELONG LOVE OF EVERYTHING SCIENCE.

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A1	primary auditory cortex
AAF	anterior auditory field
AEG	anterior ectosylvian gyrus
AES	anterior ectosylvian sulcus
AESc	cortex surrounding AES
AEV	visual field AES
Aid	agranular insular area, dorsal division
AII	secondary auditory cortex
AIP	anterior intraparietal area
AIv	agranular insular area, ventral division
ALLS	anterolateral lateral suprasylvian (visual) area
AMLS	anteromedial lateral suprasylvian (visual) area
AS	anterior sylvian area of the insula
DD	deep dorsal nucleus of MGN
DI	dysgranular insular area
DIP	dorsolateral prefrontal sector.
DLPFC	dorsolateral prefrontal cortex.
DLS	dorsal lateral suprasylvian (visual) area
dMGN/D	medial geniculate nucleus, dorsal division
DmP	dorsomedial prefrontal sector
DS	dorsal superficial nucleus of MGN

DZ	dorsal auditory zone
ED	posterior ectosylvian gyrus, dorsal part
EI	posterior ectosylvian gyrus, intermediate part
EPp	field of the posterior ectosylvian auditory cortex
EV	posterior ectosylvian gyrus, ventral part
FAES	auditory field AES
GI	granular insular area
IC	inferior colliculus
In	insular cortex
LIP	lateral intraparietal area
LM	lateralis medialis nucleus
LP	lateralis posterior nucleus, pulvinar complex
MD	mediodorsal nucleus
MGN	medial geniculate nucleus
MIP	medial intraparietal area
mMGN/M	medial geniculate nucleus, medial division
MZ	multisensory zone of AEG
P	posterior auditory cortex
PEG	posterior ectosylvian gyrus
Pi	Parainsular cortex
PLLS	posterolateral lateral suprasylvian (visual) area
PMLS	posteromedial lateral suprasylvian (visual) area
PO	posterior thalamic region
Pol	lateral posterior group of the thalamus
PoM	medial posterior group of the thalamus

PS/Ps	posterior suprasylvian (visual) area
pSTS	polysensory superior temporal sulcus,
RP	rostral pole of MGN
RSS	rostral suprasylvian sulcus
S1	primary somatosensory cortex
SC	superior colliculus
Sg	suprageniculate nucleus
SIV	fourth somatosensory area
SV	fifth somatosensory area
Te	temporal auditory area
VA	ventral anterior nucleus
Ve	ventral auditory area
VIP	ventral intraparietal area
VL	ventral lateral nucleus
vlMGN	medial geniculate nucleus, ventrolateral portion
VLPFC	ventrolateral prefrontal cortex
VLS	ventral suprasylvian (visual) area
VM	ventromedial nucleus
vMGN/V	medial geniculate nucleus, ventral division
VP/VPA	ventral posterior auditory area

PROLOGUE

Studying multisensory networks and relating neural activity to perception and behavior is of great interest to the neuroscience community. Unique external events can frequently be described by more than one sensory cue and the central nervous system is tasked to properly integrate (or segregate) these sensory signals, which often leads to a variety of perceptual and behavioral benefits. These benefits are the result of circuit computations in a complex and distributed network of brain regions. Elucidating the neural substrates of multisensory processing in the context of network activity is in its infancy stages. The following thesis attempts to begin to elucidate features of multisensory networks and their underlying neural assemblies. Special emphasis was put on characterizing neural activity to audiovisual stimulation while systematically changing stimulus properties such as spatial locating, timing, and relative effectiveness in order to highlight the relationship between external cues and multisensory processing. Furthermore, similarities and differences between classical association and primary cortices were explored in order to gain first insight into multisensory network characteristics. Their unique inputs and outputs provide differential substrates for multisensory interactions, which in turn are the building blocks for a variety of perceptual, behavioral, and cognitive processes. Understanding multisensory integration in the context of neural assemblies across the brain will shed light into the contributions of multisensory processing to perception and behavior. Laminar analysis was thus employed to investigate potential cortical and thalamic contributions to multisensory interactions as well as to delineate between feed-forward and feedback processing. The subsequent chapters are organized as follows.

Chapter 1 is a general introduction providing an overview of the field with focus on cortical multisensory processing. After a brief summary of data obtained in cat subcortex and cortex, which led to the establishment of three widely recognized principles of multisensory integration, a discussion of a set of specific brain regions in nonhuman primates and humans relates potential functional roles in perception and behavior to underlying neural activity. Two areas are specifically targeted here: insular cortex and primary auditory cortex. Findings from primates, humans, and cats are highlighted here in order to provide relevant background for the experiments undertaken within this thesis.

Chapter 2 is a very detailed review of one multisensory cortical area in cat, the anterior ectosylvian sulcus, with focus on anatomical and physiological evidence of multisensory convergence. This is of great interest as evidence from the current thesis as well as past studies revealed that this region might be an extension of insular cortex – a notion that the review brings forth, rather than being its own functional unit.

Chapter 3 and 4 encompass data from cat insula and cat A1, respectively, investigating laminar processing of audiovisual cues. As alluded to earlier, stimulus properties were parametrically varied in space, time, or effectiveness and local field potentials (LFPs) were sampled and then multisensory and unisensory LFPs were compared with the degree of interaction being dependent on stimulus parameters. Furthermore, findings suggest that multisensory interactions may be modulated by both feed-forward and feedback signals.

Chapter 5 includes an experiment in cat subcortex. Here single neurons in superior colliculus were targeted in order to investigate a potential interrelationship between stimulus features (and associated principles of multisensory integration).

Specifically, spatial location of audiovisual stimuli was varied to see if location manipulates stimulus effectiveness. Indeed, locations which elicited weak responses under unisensory conditions, showed strongest enhancements under multisensory stimulation suggestive of interdependency between the principles with the principle of inverse effectiveness maybe being the umbrella principle

Chapter 7 summarizes data collected during a battery of psychophysical experiments investigating whether or not the interrelationship between the multisensory principles is evident in human performance. Here, findings from one portion of the experiment suggest that changing stimulus saliency (a proxy for stimulus effectiveness) modulates the temporal dynamics of multisensory processing in that the period over which two stimuli are perceived as simultaneous is extended during low saliency conditions.

Altogether, findings in the current thesis highlight that there exist many similarities and some differences of multisensory processing across brain regions and even in human performance. For example, one common feature of multisensory integration is the interdependence between stimulus factors as described in the principles of multisensory integration. Moreover, multisensory interactions in association and primary cortices were brought about by interactions between signals arriving from cortex and thalamus, which may be of feed-forward or feedback nature. One difference that was observed was that audiovisual interactions in primary auditory cortex were strongly modulated by stimulus location while audiovisual interactions in insula appeared to be primarily influenced by the temporal relationship between the auditory and the visual cue. Potential implications of the current data are evaluated in the chapter 7, which encompasses a general discussion putting current findings into context of multisensory networks and their relationship to behavior and perception

CHAPTER I

GENERAL INTRODUCTION

a. Introduction to multisensory processing

Our world is made up of many different stimuli from multiple sensory modalities. The brain is well-equipped to synthesize incoming sensory information in order to create appropriate percepts of the world and initiate adaptive behaviors. Unique external events can frequently be described by more than one sensory cue and the central nervous system (CNS) is tasked to properly integrate (or segregate) these sensory signals, which often leads to a variety of perceptual and behavioral benefits such as reduction of uncertainty (Battaglia et al., 2003; Deneve & Pouget, 2004; Papandreou et al., 2009), increased stimulus detection and accuracies (Frassinetti et al., 2002; Hairston, Laurienti, et al., 2003; Lovelace et al., 2003), decreased reaction or response times (Amlot et al., 2003; Frens et al., 1995; Hairston et al., 2006; Hershenson, 1962), and improved object recognition (Amedi et al., 2005; Giard & Peronnet, 1999; Stevenson & James, 2009; Yuval-Greenberg & Deouell, 2007). In addition, numerous studies have documented multisensory benefits during complex cognitive processes such as learning (Shams & Seitz, 2008), language acquisition (Massaro, 2004), and speech comprehension (Mottonen et al., 2004; Skipper et al., 2007; von Kriegstein, 2012). Research characterizing such behavioral improvements spans a wide array of techniques (i.e. behavioral evaluations, EEG, fMRI) in order to connect psychophysical performance and underlying neural activity and much headway has been made to identify specific multisensory networks and their roles in cognition and behavior.

Much headway has been made in normal development and work has begun to elucidate the role of multisensory processing and potential changes to it in clinical populations. Indeed, extending research from the healthy population to clinical studies has revealed multiple alterations in a variety of disorders (for example dyslexia (Wallace, 2009), dementia (Sanchez et al., 2013), schizophrenia (Tseng et al., 2015), autism spectrum disorder (Marco et al., 2011),which span anything from diminished multisensory integration and behavioral gains (Harrar et al., 2014; Stevenson, Siemann, Woynaroski, et al., 2014b; Williams et al., 2010) to stimuli to changes in multisensory temporal processing (Baum et al., 2015; Stevenson, Siemann, Schneider, et al., 2014; Wallace & Stevenson, 2014).

While these studies give some insight into multisensory processes at the perceptual level and demonstrate important functions of multisensory networks in humans, studies in animal models have investigated multisensory integration in single and groups of neurons in order to establish the underlying mechanistic substrates. The next few sections will summarize key findings in subcortical and cortical multisensory regions, establish a set of working principles within which multisensory neurons as well as neural assemblies operate, and relate these findings back to observations in humans.

Some operational terminology

For the purpose of the current thesis, multisensory integration encompasses any interaction brought about by convergence of multiple sensory signals but often is marked at the single neuron level by the active integration of more than one modality resulting in a non-linear product (e.g. when measuring spike count). Overt multisensory neurons denote neurons that respond to more than one modality (i.e. bimodal or trimodal).

Modulatory multisensory neurons encompass neurons, which are only responsive to one modality but are significantly influenced by another. Some papers refer to these interactions as subthreshold modulations.

Effects of multisensory integration can be observed in response enhancement (significantly larger response during multisensory compared to unisensory stimulation), response suppression (significantly smaller response during multisensory compared to unisensory stimulation, which is still above baseline firing), and response depression (significantly smaller response during multisensory compared to unisensory stimulation, which is below baseline firing). Two common calculations are undertaken to quantify multisensory interactions, comparison of multisensory response to maximum unisensory response, termed integrative index (ii), and/or comparison of multisensory response to the additive model derived from the unisensory responses, termed multisensory contrast (msc; for a detailed review of methods see (Stevenson, Ghose, et al., 2014)).

b. Studies in cat superior colliculus and the establishment of the principles of multisensory integration

Most studies to date have been carried out in the cat superior colliculus (SC) – a multisensory subcortical structure. Cat SC has a stereotypic architecture of seven layers: three superficial and four intermediate and deep layers (Lund, 1972). It contains visual, auditory, and somatosensory neurons with ~60% actively integrating more than one modality (Gordon, 1973; Jassik-Gerschenfeld, 1965; McIlwain & Buser, 1968; Meredith & Stein, 1983; Stein & Arigbede, 1972; Sterling & Wickelgren, 1969; Wickelgren, 1971). Its strong connections with motor cortex, sensory cortex, inferior colliculus, thalamus, and brainstem (Lund, 1972) make it an ideal candidate to study sensory integration and relate it to an overt behavior. Indeed, SC has been shown to play a crucial role in head and eye orientation (Henkel & Edwards, 1978; Roucoux et al., 1980; Sprague & Meikle, 1965; Stein et al., 1976; Stryker & Schiller, 1975) and a large portion of sensory neurons also have a motor component with visual-motor neurons being the most prevalent (Sparks, 1986; Sparks & Jay, 1986).

The multisensory and sensory-motor neurons are primarily located in the intermediate and deep layers. Studies have focused there to investigate the physiological characteristics of multisensory integration (Meredith & Stein, 1983; Stein & Stanford, 2008) with the most notable studies establishing a set of working principles for multisensory neurons, which have subsequently been shown to be valid in various cortical regions within the cat and primate brain.

The principle of spatial coincidence

The concept that multisensory neurons respond differently for spatially coincident than to spatially separate cues was first established in cat SC. In fact, Meredith and Stein demonstrated that multisensory stimuli produce response enhancement when placed within the overlapping receptive fields (RF) of the constituent unisensory components (even when stimuli are not at the exact same location) and response depression or no integration outside of the RFs (Meredith & Stein, 1986a, 1996). This phenomenon has been shown in other cortical regions in the cat (Stein & Wallace, 1996; Wallace et al., 1992), in other animal models (Wallace et al., 1996) as well as in humans (Bolognini et al., 2005).

The principle of temporal congruency

If spatial location affects multisensory integration, it can be hypothesized that the temporal relationship of the stimuli might also modulate multisensory responses. Indeed, Meredith and colleagues (Meredith et al., 1987) established that multisensory neurons in cat SC integrate component unisensory signals over a range of stimulus onset asynchronies (SOAs) with one or two SOAs usually eliciting the strongest gain. This is generally dependent on the peak firing of the neuron to each unisensory cue and maximum enhancement is reached if stimuli are paired so that peak discharges overlap. Furthermore, increasing temporal offset may result in response depression. This range of stimulus disparity within which signals are integrated is most likely brought about by the fact that different sensory signals propagate at different speeds. Again, this feature appears to be a general principle extending to primates (Wallace et al., 1996) and humans (Bolognini et al., 2005). In humans, the concept of a temporal binding window (TBW) has been used to describe the binding of two stimuli into a single percept (Wallace & Stevenson, 2014). Here, research has shown that perceiving two sensory stimuli as synchronous and originating from one external event is dependent on the temporal relationship of the stimuli (Bolognini et al., 2005; Colonius & Diederich, 2004; Conrey & Pisoni, 2006; Conrey & Pisoni, 2004; Diederich & Colonius, 2009; Hairston, Burdette, Flowers, & Wallace, 2005; Hairston, Laurienti, et al., 2003; van Eijk et al., 2008; van Wassenhove et al., 2007). Interestingly, this perceptual phenomenon parallels findings at the single neuron level where integration has also been observed over several SOA creating a temporal integration curve reminiscent of the TBW (Meredith et al., 1987).

The principle of inverse effectiveness

One major feature of multisensory integration is the idea that having a second sensory modality aids the most when the original signal is weak or ambiguous. Stimulus efficacy is thus something that modulates multisensory processing substantially. Again, data from cat SC reveals that neurons exhibit the strongest response enhancements with subthreshold stimulus parameters (defined as unisensory stimuli that elicit a minimal response on their own, (Meredith & Stein, 1983)). Hence, combining two weakly effective unisensory stimuli will more often lead to response gains and conversely, combining strongly effective stimuli can lead to response suppression. This principle was also observed in neuronal response gains in other animal species, such as primates (Wallace et al., 1996) and in human behavioral gains (Bolognini et al., 2007; Hairston, Laurienti, et al., 2003; Nidiffer et al., 2015 (in revision)).

Do these principles influence each other?

Thus far, these principles were studied in isolation, yet real world stimuli are often complex in nature and have complex and entwined spatial and temporal features. As mentioned earlier, multisensory information strongly shapes perception and behavior and stimulus factors heavily modulate multisensory processing. The fact that these characteristics co-occur in real world stimuli suggests that they may influence each other in a co-dependent fashion. Indeed, recent research indicates strong interactions and interdependencies within the principles observed in neuronal data (see chapter 5 of the current thesis (Krueger et al., 2009) and (Carriere et al., 2008; Ghose & Wallace, 2014; Royal et al., 2010; Sarko et al., 2012)) as well as in human performance (see chapter 6 of the current thesis (Krueger Fister et al., 2015 (in rivision)) and (Nidiffer et al., 2015 (in revision); Stevenson, Fister, et al., 2012)). Data analysis looking at these interactions implies that spatial and temporal features of a stimulus merely affect its efficacy, which consequently would greatly influence neuronal responses and multisensory integration as defined by the principle of inverse effectiveness (Sarko et al., 2012). Nevertheless, further research is required to parcel out the exact contributions of each of these stimulus factors to the processing of the other factors and their influences on multisensory integration. Gaining insights into these mechanisms and subsequently better approximating real world stimuli may open new avenues to investigating complex human perception and behavior in the healthy populations as well as in disorders.

Chapter 5 and 6 explore the interrelationship between these principles in support of the idea that principle of inverse effectiveness may be the governing principle determining the magnitude of multisensory gains or interaction.

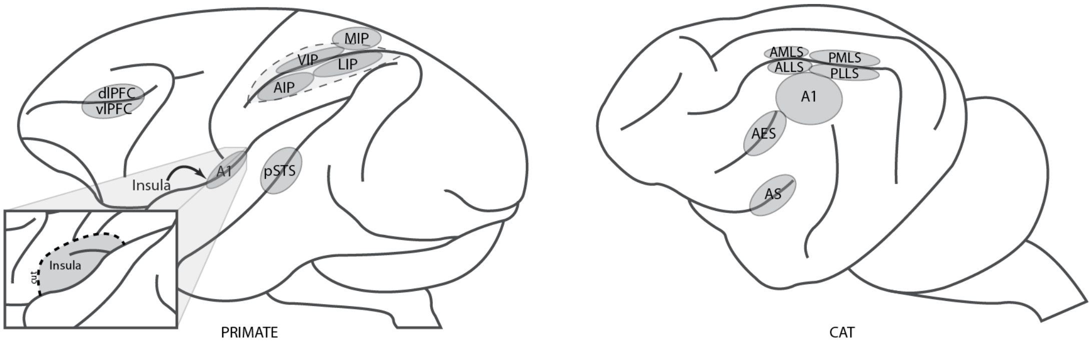


Figure 1-1: Lateral view of primate brain (left) and cat brain (right) depicting relevant multisensory regions as discussed in text. Abbreviations: see abbreviation list.

c. Studies investigating multisensory processing in cat cortex

Although, subcortical processing is undoubtedly important and has clearly revealed a set of principles that characterizes multisensory neurons, it only begins to explain how multisensory processes shape and impact perception and behavior. Indeed, assemblies of cortical neurons work within very localized microcircuits to larger multi-area networks. Some regions processes sensory information to build a representation of our external world, other regions combine these signals with internal cues, and yet others integrate all of these to guide actions and cognition. Many areas of the CNS take on several of these functions, and several (if not all) are considered multisensory.

A multitude of animal studies have built an anatomical framework for multisensory cortical networks (see chapter 2 and (Clasca et al., 2000; Nakai et al., 1987; Reinoso-Suarez & Roda, 1985; Scannell et al., 1995; Seltzer & Pandya, 1978)), with primate studies often focusing on temporal, parietal, and frontal cortices (Seltzer & Pandya, 1994). Moreover, early research has looked at physiological characteristics of specific structures within those regions but most often emphasis was put on unisensory processing or simply mapping these areas. For many structures, magnitude or features of multisensory integration have just begun to be investigated (for a review of the state of the field see (Stein & Stanford, 2008).

To date, basic features of multisensory cortical neurons have been investigated primarily in cat anterior ectosylvian and suprasylvian sulci. Both, overt multisensory neurons and modulatory multisensory neurons were characterized in these regions suggestive of different multisensory mechanisms. Experiments designed to relate neuronal changes to behavioral or perceptual effects were mostly undertaken in nonhuman primates. Areas that were of particular interest include the superior temporal sulcus, the intraparietal sulcus, the insular cortex, and the prefrontal cortex. Each one has been implicated in specific functional roles and current research is exploring how multisensory interactions contribute to those roles. Figure 1-1 shows an illustration of a cat and a primate brain (lateral surface) delineating the locations of the various areas that will be discussed next.

Anterior ectosylvian sulcus

Thus far, the cortex surrounding anterior ectosylvian sulcus (AESc) is the most studied multisensory cortical region in the cat. Chapter 2 of the current thesis is dedicated to findings in AESc but a short summary is provided below.

AESc is located within the parietotemporal cortex and is comprised of three distinct unisensory zones: the auditory field AES (FAES, (Clarey & Irvine, 1990a, 1990b)), the anterior ectosylvian visual area (AEV, (Benedek et al., 1988; Mucke et al., 1982)), and the fourth somatosensory area (SIV, (Clemo & Stein, 1982, 1983)), as well as multisensory domains at the respective overlapping unisensory representations (Jiang et al., 1994b; Wallace et al., 1992).

As demonstrated in SC, AESc neurons also actively integrated multisensory cues, giving rise to non-linear products (Wallace et al., 1992). Furthermore, this sulcus is of particular interest as it has strong connections, among others, with SC and thus is part of a sensorimotor loop (Wallace et al., 1993), forming a network linking multisensory processes to an observable behavior. In fact, studies have shown that deactivating AES impedes successful integration of multisensory stimuli within the SC (Alvarado et al., 2007; Jiang et al., 2006; Jiang et al., 2001; Stein et al., 2002) and subsequently alters approach and orientation behaviors thought to be mediated by the SC so that accuracy gains with spatially coincident stimuli as well as response inhibitions associated with spatially disparate stimuli are significantly reduced (Jiang et al., 2002; Jiang et al., 2007).

As mentioned earlier, multisensory integration in AESc has also spurred a set of studies detailing the interdependence between the multisensory principles (Carriere et al., 2008; Royal et al., 2009) where AESc has been shown to have heterogeneous spatial RFs (SRFs) wherein stimulus locations eliciting weak unisensory responses, reveal the greatest response enhancement during combined stimulation (Carriere et al., 2008). Additionally, neurons showed unique temporal patterns varying with spatial location of the stimuli (STRFs) and thus further modulating multisensory integration leading to reduced latencies and longer discharge durations for example (Royal et al., 2009).

Very recently, Dehner and colleagues demonstrated modulatory interactions between somatosensory and auditory neurons of AESc where activity of a somatosensory neuron was reduced with the addition of an auditory stimulus or vice versa (Dehner et al., 2004; Meredith et al., 2006). These subthreshold mechanisms were mediated through excitatory-inhibitory mechanisms but a follow up study illustrated that modulatory interactions are not limited to just excitatory-inhibitory interactions as first believed. Auditory AESc neurons in fact showed response enhancements during audiovisual trials (Meredith & Allman, 2009) suggesting excitatory-excitatory integration during multisensory modulation similarly to overt multisensory neurons.

Suprasylvian sulcus

Cat suprasylvian sulcus encompasses somatosensory (rostral portion) and extrastriate visual (middle and caudal portion) regions. Bimodal neurons have been identified at the border regions as well a scattered along the lateral suprasylvian sulcus (Stein et al., 1993; Yaka et al., 2002). Projections from somatosensory, auditory, and visual cortical regions were identified in the rostral suprasylvian cortex with patches of sensory convergence, which was further supported by electrophysiological recordings but non-linear interactions were rarely observed (Clemo et al., 2007). Later studies began to detail a novel multisensory mechanisms evident in subthreshold multisensory modulatory effects (Meredith et al., 2009). Anatomical connectivity analysis revealed strong projections from secondary and tertiary auditory regions to posterolateral lateral suprasylvian sulcus (PLLS; (Clemo et al., 2008)), which could be driving these modulatory effects. Allman and colleagues identified auditory influences on visual neurons in PLLS, which were providing stimulus feature information rather than simply altering arousal states (Allman, Keniston, et al., 2008) supporting modulatory interactions to be another mechanism of multisensory integration. Similar modulatory effects have been observed in other unisensory regions in primates for example and will be discussed later.

d. Studies investigating multisensory processing in primate (and human) cortex

Multisensory cortical processes have been mostly studied in the primate brain and so far, research has primarily focused on identifying regions that respond to multiple sensory signals and some headway has been made identifying whether or not these areas actively integrate multisensory cues. Studies involving the cortex surrounding superior temporal sulcus (STS), several intraparietal areas (IP), and the prefrontal cortex (PFC) demonstrated that they are involved in for example face-voice integration (STS, ventrolaterlal PFC), sensory object assessments (ventrolateral PFC), processing of spatial features of objects (dorsolateral PFC), speech perception (STS), (multi)sensory space representations and receptive field matching (ventral IP), sensory-coordinate transformations for occulomotor (lateral IP) as well as reaching and grasping planning (medial IP), object tracking and shape perception (anterior IP) and that they display multisensory interactions but the exact contributions of multisensory processes to behavior and perception have not been established.

As will be discussed in the following sections, multisensory interactions span a variety of cortical areas along the processing hierarchy. The current thesis work centers on experiments involving insula and primary auditory cortex of the cat, as two examples of cortical regions of different processing levels with potentially differential multisensory properties. The following paragraphs will briefly review multisensory key areas in the primate brain, their anatomical connections, and their proposed functional roles in order to highlight the effects of multisensory processing on perception and behavior. Subsequently to that will be a more thorough review of findings in human and primate insula as well as evidence supporting early multisensory interactions in primary sensory cortices to go with the theme of the thesis.

Superior temporal sulcus (STS)

STS is located within the temporal lobe in the primate brain. STS is made up of several extrastriate visual regions (Galaburda & Pandya, 1983) as well as one multisensory area (pSTS) in the upper bank. Indeed, pSTS was recognized as a region of sensory overlap with interactions between visual and auditory cues at the single neuron level (Benevento et al., 1977; Hikosaka et al., 1988). Generally, STS has strong connections with auditory cortex, parahippocampal regions, cingulate gyrus, insula, intraparietal sulcus, inferiotemporal areas, and prefrontal and frontal cortex (Galaburda & Pandya, 1983; Hackett et al., 1999; Seltzer & Pandya, 1978, 1994; Seltzer et al., 1996).

Multisensory STS neurons include bimodal and trimodal populations responsive to visual, auditory, and somatosensory stimulation and their combinations (Hikosaka et al., 1988). They show a strong preference for biologically relevant stimuli such as dynamic faces, vocalization, and biological motion. Indeed, studies in humans and primates implicate STS in face and voice processing (Abbott et al., 1996; Calvert & Campbell, 2003; Chandrasekaran et al., 2011; Ghazanfar et al., 2005; Kawashima et al., 1999; Mikami et al., 1994; Stevenson et al., 2011) as well as perception of biological motion (Bruce et al., 1981; Lappe et al., 1996; Maier et al., 2008; Pasternak & Merigan, 1994; Pekel et al., 1996).

Functional MRI studies have shown that STS adheres to the principles of multisensory integration and for example demonstrate activity changes as predicted by the principle of inverse effectiveness with parametrically changed stimulus efficacy (Stevenson & James, 2009). Further in line with that, STS activity is greatly modulated by changes in contextual congruency and temporal synchrony. For instance Calvert and colleagues illustrated that semantically congruent audiovisual speech stimuli lead to superadditive responses and semantically incongruent lead to subadditive activity (Calvert et al., 2000) suggestive that STS is involved in identifying contextually matched stimuli (Stevenson et al., 2009). STS has also been implicated in temporal processing during communication, particularly in synchrony judgments where specific subregions of STS responded differently for synchronous and asynchronous speech stimuli (Stevenson et al., 2010). In addition to these roles, STS may be a locus for bimodal representations of observed actions (Barraclough et al., 2005) .

Intraparietal sulcus (IPS)

The intraparietal cortex contains several structures implicated in multisensory processing. As the name suggests, IP cortex surrounds intraparietal sulcus (IPS), which is well situated between sensory, prefrontal and frontal cortices. In fact, a series of anatomical tracer studies demonstrated that IPS has strong connections with visual, somatosensory, and motor areas (Colby et al., 1993b; Grefkes & Fink, 2005; Matelli et al., 1986; Rizzolatti et al., 1998) and seminal physiology studies have established IPS to contain neurons active during sensory and spatial components of goal-directed movements such as reaching, grasping, and saccades (Duhamel et al., 1992; LaMotte & Mountcastle, 1975; Mountcastle et al., 1975).

Ventral IP (VIP) has been indicated to play a role during visual motion processing with neurons being strongly driven by direction of movement and may contribute to movements associated with defense or avoidance behaviors (Colby et al., 1993a, 1993b; Cook & Maunsell, 2002; Grefkes & Fink, 2005). Recent research has focused on identifying multisensory interactions within VIP and demonstrated vestibular-visual and somatosensory-visual interactions whereas neurons were responsive to bimodal stimuli that had RFs in close spatial register (Avillac et al., 2007; Bremmer et al., 2002; Chen et al., 2011; Duhamel et al., 1998; Schlack et al., 2002). Furthermore, Schlack et al in 2005 showed that VIP neurons are responsive to auditory in addition to visual stimulation (Schlack et al., 2005). Although auditory and visual RFs were generally well aligned, most bimodal neurons encoded space in their native reference frames (auditory – head-centered and visual – eye-centered) and yet multisensory interactions could be observed. Whether or not these neurons actively integrate these sensory modalities remains unclear. Altogether, these findings demonstrate that VIP may play an integral role in multisensory coordinate transformations as seen during peripersonal space and movement processing, in particular during tasks requiring shifts within modality specific reference frames. In general, coordinate transformation refers to the process of placing spatial coordinates in a common system to account for frames of reference unique to each sensory system. This is further of relevance when sensory information is transformed into motor behavior such as reaching or saccades.

Lateral IP (LIP) and medial IP (MIP) both have been linked to transforming coordinate frames across sensory modalities in order to accommodate receptive fields (Grefkes & Fink, 2005). LIP in particular has been strongly implicated to play a contributing role in saccade circuits (Bracewell et al., 1996; Colby et al., 1993a; Colby et al., 1996; Li et al., 1999; Mazzoni et al., 1996). MIP has been considered to be part of the parietal reaching region (PRR, (Cohen & Andersen, 2002)), which is activated by auditory and visual stimuli (Cohen, 2009; Cohen et al., 2002). Multisensory integration has not been overtly studied but both areas have been demonstrated to be responsive to auditory cues (in addition to their well-established role in visual processing, (Cohen et al., 2004)), particularly in context of a saccade task or goal-directed movements (Cohen, 2009), even though sensory spatial representation was not as strong as expected (Mullette-Gillman et al., 2005). Anterior IP (AIP) is less well studied but has been shown to be particularly active during manipulations of 3D objects (Grefkes & Fink, 2005; Joanne Jao et al., 2014; Murata et al., 2000) and has been demonstrated to integrate visual and motor signals (Sakata et al., 1995).

Prefrontal cortex (PFC)

PFC has extensive connections from sensory cortices and strong projections to the motor cortex and areas involved in cognitive processes (Barbas, 1995; Miller & Cohen, 2001) making it a crucial hub for cognitive control, complex behaviors, working-memory, and combining internal and external cues (Arnsten & Rubia, 2012; Davidson et al., 2000; Du et al., 2013; Hutcherson et al., 2012; Kane & Engle, 2002; Miller & Cohen, 2001; Quirk & Beer, 2006). Two regions within PFC, the ventrolateral PFC (VLPFC) and the dorsolateral PFC (DLPFC) have been of particular interest to multisensory research. These regions receive information from visual, somatosensory, auditory, and other multisensory regions (Barbas & Pandya, 1989; Barbas et al., 2011; Goldman-Rakic & Schwartz, 1982; Petrides & Pandya, 2002; Romanski, 2012; Schwartz & Goldman-Rakic, 1982), with unisensory projections often overlapping (Chavis & Pandya, 1976).

VLPFC has been associated with audiovisual memory retrieval (Plakke et al., 2013; Plakke et al., 2015), processes involving behavioral inhibition during multisensory learning (Rygula et al., 2010), visual object recognition (Rainer et al., 1999), reward prediction within sensory-motor tasks (Asaad & Eskandar, 2011; Pan et al., 2008), sensorimotor and reference frame transformations (Amemori & Sawaguchi, 2006; Fuster, 1990), and decision making during audiovisual stimulation (Murray et al., 2012; Plakke et al., 2015). Research has further illustrated that VLPFC neurons are responsive to visuo-spatial cues and to conspecific vocalizations (Romanski & Goldman-Rakic, 2002). VLPFC neurons actively integrate audiovisual stimuli (Romanski, 2007) with strong preferences for interactions of face and vocalization stimuli (Romanski & Diehl, 2011; Romanski et al., 2005; Sugihara et al., 2006). Moreover, neurons abide by the principles of multisensory integration exhibiting enhancement as well as suppression as seen in spike firing changes depending upon stimulus efficacy (Sugihara et al., 2006).

DLPFC's roles also include sensorimotor integration (Amemori & Sawaguchi, 2006; Bullock et al., 2015; Fuster, 1990), integration of sensory and motivational processes (Amemori et al., 2015; Sakagami & Watanabe, 2007), sensory-driven memory-related activity (Gonzalez-Burgos et al., 2005; Katsuki & Constantinidis, 2013; Plakke et al., 2013; Plakke et al., 2015), reward assessments and subsequent motor behavior (Pan et al., 2008; Wallis & Miller, 2003), and learning and decision making (Lee & Seo, 2007). While these functions undoubtedly span multiple senses, to date multisensory contributions to these functions have not been specifically investigated.

Although, VLPFC and DLPFC have many overlapping functional utilities, one major difference between them is that VLPC neurons encode object features, while DLPFC neurons are thought of to encode spatial features (Romanski, 2004), making them part of what and where processing streams, respectively (Wilson et al., 1993). Interestingly, research suggests that information of these dual streams is represented across modalities (Romanski et al., 1999), is integrated with motor behaviors (di Pellegrino & Wise, 1993),and thus PFC may be linking sensory information with motor outputs across these two processing streams (Rao et al., 1997).

e. The insular cortex - linking sensory integration and perception and behavior

Of great interest is the insula as it is thought of as a candidate region of strong sensory and cognitive convergence. Indeed, the role of insular cortex appears to span a host of functions ranging from basic sensory processing to emotions, self-awareness, speech and motor functions, as well as cognitive control. Moreover, several studies undertaken in humans, non-human primates and other species (for example the cat) have identified the insula to be active during multisensory stimulation, which is of particular interest as one could hypothesize the insula to play a critical role in (multi)sensory-cognitive integration and thus may provide insight into the contributions of multisensory networks to perception and behavior.

Human insula is located deep within the Sylvian fissure and is comprised of three zones: a rostroventral agranular domain, a caudodorsal granular domain, and an intermediate dysgranular zone (Friant, 1956; Gallay et al., 2012; Mesulam & Mufson, 1985; Morel et al., 2013; Nieuwenhuys, 2012). Additionally, anterior insula houses an intriguing subset of neurons in layer 5 termed von Economo neurons (Allman et al., 2010; Stimpson et al., 2011), which are thought of to be part of a network involved in decisions making, social cognition, and self-awareness (Allman, Tetreault, Hakeem, & Park, 2011; Allman, Tetreault, Hakeem, Manaye, et al., 2011). Functionally, there exists an anterior-posterior axis within insula whereby anterior portions seem to be part of limbic and paralimbic networks while posterior regions belong to sensorimotor loops (Nieuwenhuys, 2012). A processing hierarchy has been proposed where sensory cues are processed first in posterior insula, then integrated with interoceptive-sensory signals from other regions in mid-insula, and eventually join limbic information being processed in anterior insula (Nieuwenhuys, 2012).

Meta-analyses in humans (Cauda et al., 2012; Cerliani et al., 2012; Chang et al., 2013; Craig, 2009; Jakab et al., 2012; Kelly et al., 2012; Kurth et al., 2010; Mutschler et al., 2009; Starr et al., 2009) and anatomical tract tracing in primates support such a segregation structurally between anterior and posterior insula (Cavada et al., 2000; Chikama et al., 1997; Mesulam & Mufson, 1985; Mufson et al., 1997). Of note here though, primate insula has been demonstrated to be comprised of at least 8 subregions (Gallay et al., 2012) and human anterior insula may not have a clear primate homologue (Craig, 2009). Nevertheless, both primate and human insula indeed have extensive connections with dorsal thalamus, sensory and association cortex, amygdala and other limbic regions, premotor cortex, and ventral striatum (Nieuwenhuys, 2012) while insular subregions are greatly interconnected (Friedman et al., 1986).

Functional role: evidence from primate and human studies

As briefly stated earlier, the insula is thought of as a crucial node within networks involving sensory processing, signal saliencies, task switching, attention and executive control functions, social and emotional domains, speech, sense of self, as well as working memory (for a few general reviews see (Chang et al., 2013; Jones et al., 2010; Kurth et al., 2010; Menon & Uddin, 2010; Mutschler et al., 2009; Nieuwenhuys, 2012; Ohira, 2014)). As such a neural hub, it comes as no surprise that one of the more prevalent functions of insula is to integrate extero- and interoceptive cues.

1. Sensory processing

Studies in primates have shown that neurons in the insula respond to auditory (pure tones, natural calls; (Bieser, 1998)), visual (visual pattern motion, fast moving stimuli; (Benevento et al., 1977; Grusser et al., 1990a; Thorpe et al., 1983)), somatosensory (innocuous and nociceptive stimuli, temperature; visceral and proprioceptive stimuli (Craig, 2003; Robinson & Burton, 1980a, 1980b; Schneider et al., 1993; Zhang et al., 1999)), olfactory (often parts of the insular are designated olfactory cortex; (Rolls & Baylis, 1994; Tanabe et al., 1975; Tanabe et al., 1974)), gustatory (taste-specific as well as oral stimulation related to food texture; (Bagshaw & Pribram, 1953; Rolls, 2015; Rolls & Baylis, 1994; Yaxley et al., 1990)), and vestibular (Grusser et al., 1990b) signals. Of notable importance is that most of the aforementioned findings (and other studies) also highlight that insular neurons are frequently activated by two or more sensory stimuli (Benevento et al., 1977; Grusser et al., 1990a; Rolls & Baylis, 1994; Shinder & Newlands, 2014; Thorpe et al., 1983) suggesting integrative properties within insular circuits. In line with the anterior-posterior axis, sensory-responsive regions are primarily located in the posterior portion of insula (Nieuwenhuys, 2012).

Research in humans parallels findings in primates in that human insular cortex too gets stimulated by aforementioned sensory stimuli (auditory (Bamiou et al., 2003; Habib et al., 1995; Tamura et al., 2015), visual (Simmons et al., 2004; Simmons et al., 2006), somatosensory and pain (Brooks et al., 2005; Burton et al., 1993; Frot et al., 2007; Garcia-Larrea, 2012; Ostrowsky et al., 2002; Pugnaghi et al., 2011; Segerdahl et al., 2015), visceral (Penfield & Faulk, 1955; Stephani et al., 2011), olfactory (Gottfried & Zald, 2005; Heining et al., 2003; Penfield & Faulk, 1955), gustatory (Avery et al., 2015; Henderson et al., 2011; Rudenga et al., 2010; Small, 2010; Stephani et al., 2011), and vestibular (Fasold et al., 2002; Kirsch et al., 2015; Mazzola et al., 2014)).

Some studies do reveal sensory convergence and multisensory interactions in human insula (Frank et al., 2014; Hashimoto et al., 2013) and case reports of patients with damage to the insula highlight its multisensory properties showcasing symptoms such as visual or auditory neglect, as well as oral and motor apraxia (Berthier et al., 1987; Tamietto et al., 2015). Yet, direct testing of multisensory integration in the insula has been sparse. A few studies have looked at stimulus congruency effects encompassing temporal, spatial, and contextual factors (audiovisual integration (Moris Fernandez et al., 2015; Naghavi et al., 2007; Teder-Salejarvi et al., 2005) and visuo-tactile integration (Zeller et al., 2015)), linear versus non-linear interactions (visuo-tactile integration (Gentile et al., 2011)), and illusory percepts such as the ventriloquism effect or the rubber hand illusion (Bischoff et al., 2007; Zeller et al., 2015).

2. Motor and speech production

Strong evidence of involvement in motor behaviors is derived from insular stimulation as well as fMRI studies in humans. Both visceromotor (specifically related to the gastrointestinal and cardiac systems) and somatomotor (hand and foot motor tasks) control have been observed. For example, stimulation or dysregulation of human insula elicited nausea and vomiting, changes in heart rate and rhythm, and respiratory arrest (Oppenheimer, 2006; Oppenheimer, 1994; Penfield & Faulk, 1955; Pollatos et al., 2007). While sensory, and visceromotor representations are primarily located within the posterior insula (Nieuwenhuys, 2012), the picture is less clear for motor regions as they have been observed in anterior and posterior insula. Indeed, posterior and anterior portions of insular cortex are frequently activated with the use of upper and lower extremities (Kurth et al., 2010; Mutschler et al., 2009), and posterior activation overlaps with somatosensory representations (Afif et al., 2010). Nevertheless some distinction can be made since activation of anterior insula often shows a ventral and dorsal division where dorsal portions process audio-motor tasks and ventral portions co-activated with amygdala and other limbic regions during motor behaviors (Mutschler et al., 2009).

Furthermore, due to its proximity to pathways connecting Wernicke and Broca's areas, insular cortex has been proposed to be involved in speech-related tasks such as coordinating pre-articulatory and articulatory processes as well as language perception (Ackermann & Riecker, 2004, 2010). Indeed, anterior portions of insula have been shown via fMRI to be part of a speech motor control network (Bohland & Guenther, 2006; Riecker et al., 2000; Riecker et al., 2005) and speech disturbances have been reported with its disruption (Afif et al., 2010). Case studies of patients with auditory aphasia confirmed that symptoms associated with changes in speech articulation were associated with damage to those particular regions in the insula (Dronkers, 1996). Yet, the exact contributions of insula to speech production remain controversial and warrant further investigations (Ackermann & Riecker, 2004, 2010). Regardless, functional connectivity analyses revealed that anterior insula is part of a preparative motor loop which also includes the supplementary motor area, the inferior frontal gyrus and superior cerebellum (Ackermann & Riecker, 2010).

Additionally, if and how sensory signal processing contribute to these described roles remains to be solved. Nevertheless, given that insular cortex features sensory representations within close proximity to subregions proposed to mediate motor and speech production, it is not far fetched to hypothesize that insula is a (multi)sensorimotor transformation node. Here it is noteworthy to say that many motor functions as well as speech are thought of to be inherently multisensory (Massaro, 2004; Skipper et al., 2007) combining for example auditory signals from the voice of a speaker with visual signals from their mouth during speech production. Furthermore, autonomic regulation and somatomotor control are likely to contribute to another insula function, body awareness, as discussed later (Critchley et al., 2004; Tsakiris, 2010).

3. Human communication

Human communication is intricate and complex and requires many different processes. Indeed, in addition to speech production and perception, understanding emotional, contextual, and behavioral cues appear crucial in such social interactions. Insular cortex has been shown to be involved in several key features of communication. Studies observed insular activation during affective speech processing and comprehension (Beaucousin et al., 2007), viewing and imitation of faces (Braadbaart et al., 2014), imitational learning like playing a guitar (Buccino et al., 2004), and empathy expressions (Bernhardt & Singer, 2012). Furthermore, damage to the insula caused auditory agnosia as well as difficulties in language production and comprehension (Habib et al., 1995). One interesting hypothesis is that insula works in conjunction with the mirror system (Rizzolatti, 2005; Rizzolatti & Craighero, 2004), which allows humans (and other species) to mimic and understand their opponent's actions and behaviors. The contributions of multisensory interactions to insula's role in human communication have yet to be determined.

4. Emotions

Anterior insula has been implicated in both processes involving internal emotional states as well as social emotions (Phan et al., 2002). Individual emotions that activate the insula include happiness (Chen et al., 2009), sadness (Eugene et al., 2003; Lane et al., 1997), fear (Linnman et al., 2011; Phillips et al., 1998; Sehlmeyer et al., 2009), and disgust (Heining et al., 2003; Jabbi et al., 2008; Krolak-Salmon et al., 2003; Sambataro et al., 2006; Sinha, 2014; Suzuki, 2010; Wright et al., 2004). Further research heavily relies on its role in pain processing. Indeed, often insular activity is strongest during the emotional portion of pain perception (Lamm et al., 2011).

Recent findings expanded insula's role in emotion processing to include social emotions such as empathy, compassion, fairness, and cooperation (Cacioppo & Decety, 2011; Gallese et al., 2004; Immordino-Yang et al., 2009; Lamm & Singer, 2010; Ochsner et al., 2008; Zaki et al., 2012). Interestingly, microstimulation of primate insula also elicited behaviors associated with basic and social emotions such as disgust and lip-smacking, which is seen as a reassuring behavior and only occurred when the monkey had direct eye contact with another individual (Caruana et al., 2011), In support of this, anatomical connectivity data places primate insula within an emotional network as part of the limbic system (Jezzini et al., 2015).

Conveying emotional cues heavily relies on sensory information like visual cues when analyzing someone's facial features, auditory cues when listening to someone's voice, and somatosensory cues when interacting with the other person. In fact, often all these sensory signals convey information from one social interaction, yet little research has been done to investigate such multisensory processes in the insula. Most findings to date come from studies of schizophrenia, which has been linked to altered integration of emotional social cues arising from dynamic faces and voice (de Gelder et al., 2005; de Jong et al., 2009; Van den Stock et al., 2011) and structural changes in the insula (Crespo-Facorro et al., 2000; Takahashi et al., 2004). Indeed, patients with schizophrenia had even diminished multisensory integration of meaningless audiovisual speech stimuli (stimuli were meaningless utterances, (de Gelder et al., 2003)) suggesting that insula may deal with both, purely sensory and more complex (emotional) cues.

5. Cognitive control: a link between external and internal worlds

Together with a variety of other regions, including the presupplementary motor area, DLPFC, the posterior parietal cortex, and the anterior cingulate cortex (ACC), anterior insula is involved in a variety of cognitive control tasks (Cole & Schneider, 2007; Nieuwenhuys, 2012). One particular interesting function related to this is that insula has been proposed to play a critical role in mediating processes involving representations of the external world and the internal state such as monitoring one own's heartbeat during various emotional states in response to viewing short video clips or holding sequences of visual stimuli in working memory in order to make a decisions regarding a specific task (Avery et al., 2015; Chang et al., 2013; Cole & Schneider, 2007; Kelly et al., 2012; Nieuwenhuys, 2012; Ochsner et al., 2008; Ohira, 2014; Zaki et al., 2012). It is hypothesize that the insula does this by sorting through incoming signals and identifying their relevance to current existing internal states. Insula has thus been suggested to form, together with ACC, a saliency network, which provides the CNS with information about the importance of external and internal stimuli in order to guide behavior (Menon & Uddin, 2010). Here, the role of insula is manifold in that it processes bottom-up sensory signals, switches attentional states to accommodate access to working memory and attentional networks, and tightly interacts with ACC to facilitate interactions with motor systems (Menon & Uddin, 2010). Multisensory contributions to this have not been characterized but one study linked activation in anterior insula to multimodal attentional control (Chen et al., 2015) indicative of insula's role in coordinating signals across the senses during behavior and perception, particularly in the context of cognitive control.

This idea of combining intero-and exteroception is further supported by insula's role in body awareness and self-perception (Tsakiris, 2010). Body ownership has been described as a multisensory experience involving visual-somatosensory integration in peripersonal space (Longo et al., 2012; Longo et al., 2008) and arising from ones' body (Gentile et al., 2011), understanding what belongs to one's body (Longo et al., 2008), and the subjective experience of body awareness (Critchley et al., 2004; Tsakiris, 2010); which separately have all been implicated to be subserved by insular cortex ((Nieuwenhuys, 2012). Indeed, evidence arising from clinical studies detail changes of self-perception and body-awareness. For example insular cortex lesions have been linked to patients' anosognosia of hemiplegia (Vocat et al., 2010), or loss of body-ownership (Cereda et al., 2002; Karnath et al., 2005).

6. Von Economo neurons (VENs)

Of particular interest when studying higher-order cognitive processes are von Economo neurons. These spindle type cells have been found in ACC as well as in the fronto-insular (insula and PFC) complex, and they have so far been studied in human as well as non-human primates (Allman et al., 2010; Nieuwenhuys, 2012; Stimpson et al., 2011). Historically, only described in hominoids, recent evidence also identified VEN versions in macaque monkeys, elephants, and some cetaceans (Butti et al., 2009; Evrard et al., 2012; Hakeem et al., 2009; Hof & Van der Gucht, 2007). In his recent review Nieuwenhuys points out that these are all species with evolved social systems, which necessitate a series of specialized emotional, and cognitive control behaviors (Nieuwenhuys, 2012).

Thus, speculations about the role of VEN in highly demanding cognitive tasks has made them an interesting target to study insular function in integrating information derived from external and internal signals. Strongest evidence again arises from clinical studies (Butti et al., 2013) involving disorders marked by changes in emotional and social cue processing. Patients with frontotemporal dementia (the behavioral variant form), early-onset schizophrenia, and damage to the insula-ACC corpus collosum connection showed marked VENs reduction (Butti et al., 2013). Whether or not VENs actively integrate or respond to multisensory stimuli remains to be elucidated. Evidence of VEN in macaques however allows for the possibility to study their properties more directly and promises to shed light onto their physiological characteristics in context of behavior and perception.

As these past sections allude to, insula function spans multiple sensory systems, involves motor and limbic networks, and links to cognitive and perceptual processing. Particularly intriguing is its proposed role of integration extero- and interoceptive cues in context of multisensory interactions. With these implications in the functional domains and with its characteristic organization connecting with regions of sensory, motor, as well as limbic fields and cognitive networks, insula is an excellent candidate region to study the contributions of multisensory integration to a variety of behavioral and perceptual processes.

Investigating multisensory interactions at the neural level is a crucial first step in characterizing how insular processes information across the senses and how said processing fits within a larger network. A large number of prior studies in cat have laid out a neurophysiological and anatomical framework for multisensory integration in subcortex and cortex, making the cat a pertinent model species for studying multisensory interactions in the insula. Furthermore, cat insula has been shown to have a similar organization as human and primate insula connecting with regions of sensory, motor, and limbic systems (Clasca et al., 1997, 2000) allowing for comparisons across species.

The next few sections will focus on briefly summarizing known anatomical and physiological features of cat insular cortex. Focus will be on one sensory subdivision of insula, the anterior sylvian area (AS), as it is particularly well-suited to study the anatomical and physiological characteristics of a multisensory circuitry in order to begin to elucidate how insula integrates multiple sensory modalities and how multisensory networks are built in general. Area AS has indeed been investigated in the current thesis and results are discussed in chapter 3.

Insular cortex of the cat

1. Connections, lamination and cytoarchitecture

Cat insular cortex is a multisensory hub with somatosensory, auditory, visual, olfactory, limbic, and nociceptive inputs. It is located within the anterior sylvian and orbital gyri ventral to anterior ectosylvian sulcus and anterior to auditory association cortex at the temporal-parietal-frontal junction of cat cortex. Clasca and colleagues to date published the most extensive set of studies of insular connection patterns. The group showed that it is comprised of six regions with distinct connections with cortex and thalamus (Clasca et al 1997, 2000). Similar subdivisions have also been shown in old world and new world monkeys, bats, ferrets, rabbits, and humans although number of regions may vary by species (Nieuwenhuys, 2012). Similar to other mammalian species, cat insula has a variety of reciprocal connections with unisensory and multisensory sensory cortices, limbic structures, entorhinal cortex, thalamus, and frontal lobe. The following section will briefly review anatomical and physiological findings in cat insula with special emphasis on studies investigating the anterior sylvian area as characterized by Clasca and colleagues.

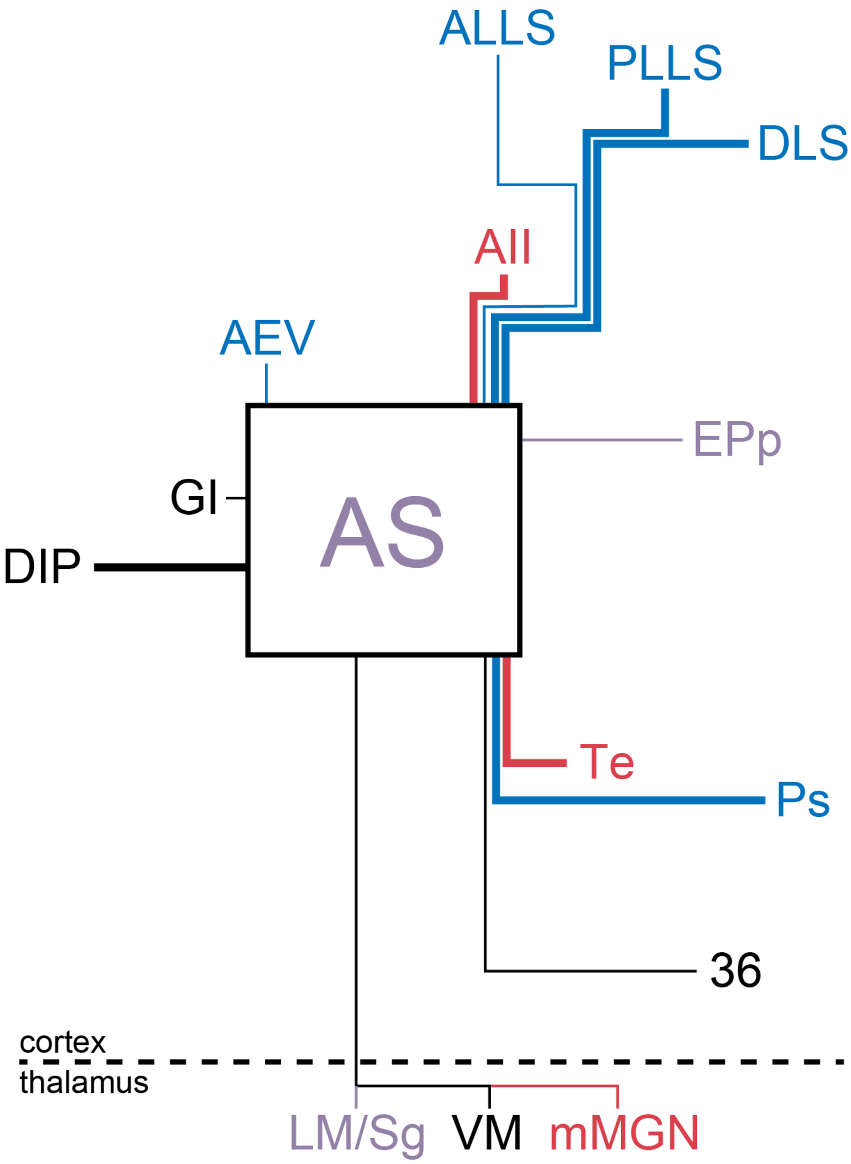


Figure 1-2: Major cortical and thalamic inputs to the anterior sylvian area of cat insula. Color conventions are as follows; auditory – blue, visual – red, multisensory – purple, and other – black. Abbreviations: see abbreviation list.

Inputs

One interesting feature between the subregions is that they receive very little overlapping inputs, suggesting that each subfield is involved in different functional circuits and roles (Clasca et al., 2000). Specifically, the granular insula (GI) is strongly connected with somatosensory, motor, premotor and prefrontal regions while the dysgranular insula (DI) receives inputs from lateral prefrontal and premotor areas, as well as lateral somatosensory and perirhinal cortices. GI also forms loops with posterior medial and ventroposterior inferior thalamic nuclei. Gustatory and viscerosensory portions of the ventroposterior complex as well as ventrolateral thalamic nuclei connect with DI (Clasca et al., 2000). The agranular insula can be divided into a dorsal (AId) and a ventral (AIv) field. AId is part of a limbic loop as well as reciprocally connects with mediodorsal, ventromedial, parafascicular and midline thalamus. AIv has strong connections with olfactory regions but only sparsely connects with thalamus (midline nuclei, (Clasca et al., 2000)). Parainsular cortex (Pi) and the anterior sylvian area (AS) are the insula regions, which receive strong inputs from sensory cortices. Pi connects with non-tonotopic auditory fields and ventromedial frontal areas as well as with caudal portions of medial geniculate nucleus (MGN). AS receives projections from auditory, visual, and multisensory regions, dorsolateral prefrontal and perirhinal cortices, and ventromedial thalamus (VM), suprageniculate nucleus (Sg), and lateralis medialis (LM) nuclei of the thalamus ((Clasca et al., 2000), see also Figure 1-2). The aforementioned connectivity patterns of these six subfields highlight a homologous organization to primate and human insula cortices in that posterior portions are connected with sensory regions while anterior portions are connected with limbic regions (Nieuwenhuys, 2012).

As alluded to above, in order to detail AS connectivity, Clasca and colleagues undertook a set of studies utilizing retrograde and anterograde tract tracing to investigate projection patterns to and from the subfields of orbito-insular cortex in cat (Clasca et al., 2000). The group identified strong cortical projections from lateral visual suprasylvian fields (PLLS, DLS, PS, and VLS), 21b, and AEV to AS. Additionally, auditory regions EPp, AII, and Te, somatosensory region ALLS, frontal eye fields DIP, and DmP also project to AS. Small patches of labeling were likewise found in cingulate cortex. Connections with contralateral cortex are sparse but include AS, AII, and AEV; as well as minor patches in PLLS, DLS, EPp, and PS. Interestingly, no contralateral connections with prefrontal or perirhinal cortices were observed. Labeling in thalamus predominantly indicated strong reciprocal connections with LM and Sg, as well as heavy projections from mMGN, and VM. Sparse labeling was also found in MD, VA-VL border, midline nuclei, vlMGN, and dMGN. Some minor projections from AS reach VM, mMGN, and the reticular thalamic nucleus as well as the ventroposterior complex.

Outputs

Generally, insula projections are widely reciprocal to its cortical and thalamic inputs. While anterior insular fields heavily interact with regions associated with sensorimotor integration of face and upper body (GI and DI), with regions of gustatory cortex (DI) and olfactory cortex (AIv), as well as with limbic cortical fields (AId), posterior areas Pi and AS both reciprocally connect to sensory fields and prefrontal cortex (Clasca et al., 2000). Yet, Clasca and colleagues concluded that only AS is a complex multisensory region of insula. This is brought about by their observations that Pi heavily interconnects with auditory fields while AS receives inputs from and projects to regions of visual and somatosensory cortex in addition to auditory cortex.

Besides its reciprocal connections with most of its cortical inputs, some areas receive heavier back-projections from AS than others. Indeed, AS heavily targets suprasylvian visual regions, which have been implicated in spatial visual processing (Hardy & Stein, 1988; Payne et al., 1996) and DIP, an area associated with visuomotor processing (Cavada & Reinoso-Suarez, 1985). Major subcortical outputs include LM and Sg of thalamus, which are both multisensory convergence sites. Other regions that receive noteworthy minor inputs from AS are perirhinal area 36, MGN and VM (Clasca et al., 2000; Hicks et al., 1986; Hoshino et al., 2010).

2. Physiology

In the cat, neuronal activity in the insula has been primarily investigated using sensory mapping techniques. Single and multiunit activity as well as local field potentials have been measured in response to auditory, visual, and somatosensory stimuli. Most of these studies were undertaken before Clasca and colleagues delineated the six subregions, but the present review will try to identify subregions where possible.

Visually-responsive neurons in the dorsal insula (which includes insular area AS and often AEV) showed large receptive fields, preferred moving visual targets and exhibited some form of dynamic direction sensitivity (Benedek et al., 1986). Benedek, Hicks, and colleagues further demonstrated that the motion speed preference varied between neurons located in superficial layers (high-velocity preference) and neurons located in the deeper layers (low-velocity preference). Moving bars elicited stronger responses than moving spots. Visuotopic organization was investigated but no clear map was identified. Visual insula neurons also appeared to be tuned to low frequency spatial drifting grating stimuli while high frequency gratings often led to inhibitory effects (Benedek & Hicks, 1988; Benedek et al., 1986; Hicks et al., 1988a, 1988b). Interestingly, this visual region described here is situated immediately ventral to AEV (Clasca et al., 1997; Norita et al., 1986; Olson & Graybiel, 1987), and exhibits similar physiological characteristics and receives overlapping inputs with AEV (Benedek et al., 1988; Clasca et al., 1997, 2000; Mucke et al., 1982; Norita et al., 1986). Some have postulated that

AEV and insula may be continuous or even that AEV is an insular subfield (see chapter 2 AES review).

Dorsal insula (again including AS) has also shown some responsiveness to auditory and somatosensory stimulation (Benedek et al., 1996; Hicks et al., 1988a), however to drive neurons in that region the stimuli often required to be at very high intensities (Hicks et al., 1988a). Other studies identified auditory frequency-dependent responses with cells most often being inhibited at the onset of the stimulus (intracellular recordings) as well as general responsiveness to click stimuli but tested regions were poorly defined and thus conclusions about insular auditory neuron characteristics are difficult to make.

Studies looking at the ventral insula are even scarcer. Here, one study, which focused on mapping sensory responses in cat insula, showed (multi)sensory responses to be clustered in the dorsal insula with a few multisensory and unisensory cells located in the ventral portion (Hicks et al., 1988a).

Utilizing local field potentials, bimodal and trimodal responses were encountered throughout the extent of the insular cortex. Trimodal activity occurred most frequently, followed by bimodal activity (particularly audiovisual responses), and unimodal activity. Multisensory integration as defined in this thesis has not been tested in cat insula (Hicks et al., 1988a).

Why should we study the cat insula, particularly the anterior sylvian area?

AS has extensive connections with unisensory and multisensory cortex and thalamic nuclei strongly suggesting sensory integrative properties. In fact as mentioned earlier, prior electrophysiological studies indeed identified bimodal cells, but active integration of multiple sensory cues has not been measured. Furthermore, insula itself is part of motor and limbic loops and is hypothesized to be a major hub for integration of extero- and interoceptive cues. In the cat, insular cortex is also located at the parieto-temporal-frontal junction presumably reflective of its role in combining information of these different regions and particularly AS is right on the surface of the brain allowing for easy localization and recordings spanning all cortical layers. Collecting data from AS and identifying mechanisms across laminae and putting them in context of network activity related to perception and behavior will allow for a more complete picture of multisensory contributions to these processes.

In addition to investigating multisensory interactions in association cortex, recent implications of modulatory interactions at the level of primary unisensory fields, warrants extending these investigations to early cortices. To date, primary auditory cortex is the most widely studied structure exhibiting non-primary sensory influences. Indeed, these findings began a debate whether or not entire cortex is essentially multisensory (Ghazanfar & Schroeder, 2006). Thus the following sections will summarize research undertaken in primary sensory areas with focus on the auditory cortex in context of modulatory multisensory interactions and their contributions to perception and behavior.

f. Multisensory interactions in primary auditory cortex

In light of increasing evidence that substantial multisensory interactions can take place much earlier in cortex than previously thought, researchers have begun to ask if all of neocortex is fundamentally multisensory. Strong support stems from evidence across multiple species and techniques identifying that activity in unisensory cortices can be modulated by non-dominant signals (for a few reviews see (Bizley & King, 2012; Foxe & Schroeder, 2005; Ghazanfar & Schroeder, 2006; Hackett & Schroeder, 2009; Kayser & Logothetis, 2007; Macaluso, 2006; Schroeder & Foxe, 2004; Schroeder & Foxe, 2005).

To date, the most progress in characterizing modulatory multisensory integration in primary cortex has been made by looking at non-auditory influences in auditory cortex. Multisensory interactions there include but are not limited to oscillatory phase-resetting by somatosensory (Lakatos et al., 2007) or visual cues (Kayser et al., 2008), increases in spatial information with the addition of a visual stimulus (Bizley & King, 2008, 2009), and enhancement of auditory activity by visual (De Santis et al., 2007) or somatosensory signals (Kayser et al., 2005; Murray et al., 2005). These early interactions could be the neural substrates for behavioral phenomena such as speeded reaction times and increased detection rates during multisensory stimulation as proposed in a study by Molholm and colleagues (Molholm et al., 2002), which correlated reduction in latencies seen in EEG data with speeded response times during an audiovisual detection task.

Of course, these modulatory interactions have not been limited to auditory cortex. Both, visual and somatosensory primary cortices have been demonstrated to be influenced by other sensory modalities. For example auditory signals enhanced visual activity (Martuzzi et al., 2007; Molholm et al., 2002), decreased response latencies (Wang et al., 2008), and reset oscillatory phase (Mercier et al., 2013; Naue et al., 2011) in primary visual cortex. Visual signals in primary somatosensory cortex have been demonstrated to add spatial-information (Taylor-Clarke et al., 2002) similarly to what has been observed in auditory cortex. Audio-tactile interactions have also been observed where the addition of an auditory cue led to an enhancement of the tactile signal compared to tactile alone (Foxe et al., 2000).

More often then not, these effects were observed in local field potentials (LFP), which may be more sensitive to subthreshold changes and thus may provide insight into alternate or supplementary mechanisms for multisensory interactions. Furthermore, LFPs are derived from changes in the electrical potential within a specific region of brain tissue (not just single unit activity) and are thought to reflect synaptic currents of multiple neurons (Mitzdorf, 1985, 1987). Thus, data derived from LFPs can extend findings to the synaptic level and may begin to elucidate the non-linear transform/gain that takes place during integration. Of interest is also their oscillatory quality, which allows investigation of potentially novel interactions visible in for example phase-resetting or phase-locking (Friston et al., 2015). All of these features become valuable when thinking about the effects of multisensory interactions on cortical micro- and macrocircuits.

Indeed, as the name implies, sources of LFPs are fairly spatially constrained around the recording electrode (Kajikawa & Schroeder, 2011; Lindén et al., 2011) and illustrate columnar/local network activity (Mazzoni et al., 2012). Collecting localized evidence of multisensory processing within a structure and then putting it in the context of a neural network (Einevoll et al., 2013) is particularly crucial as many behaviors (and perception) are derived from joined (or opposing) activity of multiple structures. Furthermore, LFPs correlate well with EEG (Buzsaki et al., 2012; Mitzdorf, 1985) and BOLD (from MRI (Logothetis et al., 2001)) measures, which are a non-invasive techniques frequently utilized to characterize neural activity in humans. In fact, comparing LFP findings to EEG data has been a recent effort to bridge studies in humans and non-human primates.

Subsequent sections will focus on briefly summarizing known anatomical and physiological features of cat primary auditory cortex. With previously discussed evidence in multisensory interactions even in primary sensory cortices in mind, the current thesis work utilized evidence from undertaken A1 experiments to compare and contrast multisensory interactions across laminae in a primary sensory cortex to an association region. Findings of the A1 experiment will be discussed in chapter 4.

Primary auditory cortex of the cat

1. Connections, lamination and cytoarchitecture

Cat primary auditory cortex (A1) is located in the temporal lobe, immediately ventral to the anterior auditory field (AAF) and the dorsal zone (DZ), and dorsal to secondary auditory cortex (AII). The posterior portion of A1 is flanked by AES and the anterior portion by the posterior ectosylvian sulcus (PES). Amongst others, Lee and Winer published a series of papers extensively delineating A1 connections with thalamus, cortex, and subcortex. Naming convention here will follow their papers.

Inputs

As expected A1 receives tonotopic projections to its granular layer from ventral medial geniculate nucleus (vMGN), which in fact, make up more than 85% of its inputs from thalamus ((Andersen, Knight, et al., 1980; Huang & Winer, 2000; Kelly & Wong, 1981; Lee & Winer, 2008c; Niimi & Matsuoka, 1979; Winer et al., 1977), see also Figure 1-3). The tonotopic rostral pole of MGN, the dorsal and medial divisions (dMGN and mMGN, including dorsal superior MGN (DS)) only sparsely connect with A1 (Andersen, Knight, et al., 1980; Huang & Winer, 2000; Lee & Winer, 2008c; Niimi & Matsuoka, 1979).

Tonotopically organized cortex connections include AAF, the posterior auditory cortex (P), the ventral auditory area (Ve), and the ventral posterior auditory area (VP), with the latter three comprising the cortex surrounding PES and AAF and P being the most robust (Lee & Winer, 2005, 2008a). Further, less strong, inputs arise from non-tonotopic secondary auditory regions, such as AII, AES, and DZ (Imig & Reale, 1980). Interestingly, A1 also receives non-auditory inputs suggestive of potential multisensory modulations. Multisensory inputs encompass domains of the posterior ectosylvian gyrus:

the dorsal PEG (ED), the intermediate PEG (EI), and the ventral PEG (EV), as well as insular cortex (In), which has also limbic properties (Imig & Reale, 1980; Lee & Winer, 2008a). Temporal cortex (Te) and perirhinal regions 35/36 make up the other limbic projections to A1 (Lee & Winer, 2008a). Lee and Winer observed interesting laminar differences; AAF and DZ project to supra- and infragranular layers, while P, VP, VE, AII, and EI only project to infragranular laminae (Lee & Winer, 2008a). Similar patterns have been described by others (Kelly & Wong, 1981).

Outputs

A1 has strong back projections to supra- and infragranular layers of AAF, P, VP, and DZ. Minor projections target infragranular layers of Ve (Imig & Reale, 1980; Lee & Winer, 2008a). A robust connection from A1 to inferior colliculus (IC) was also observed (Andersen, Snyder, et al., 1980; Diamond et al., 1969; Kelly & Wong, 1981; Winer et al., 1998; Winer et al., 2002). Reciprocal commissural connections exist between A1, AAF, AII, DZ, P, VP, and Ve (Clarke et al., 1995; Lee & Winer, 2008b). Degeneration and tract tracing studies also demonstrated A1 projections to SC, MGN (all three main divisions), Sg, pulvinar, reticular thalamic nucleus, several pontine nuclei (Bajo et al., 1995; Brodal, 1972; Diamond et al., 1969; Kawamura & Chiba, 1979; Perales et al., 2006), claustrum (Beneyto & Prieto, 2001), and the superior olivary complex (Malmierca & Ryugo, 2011)

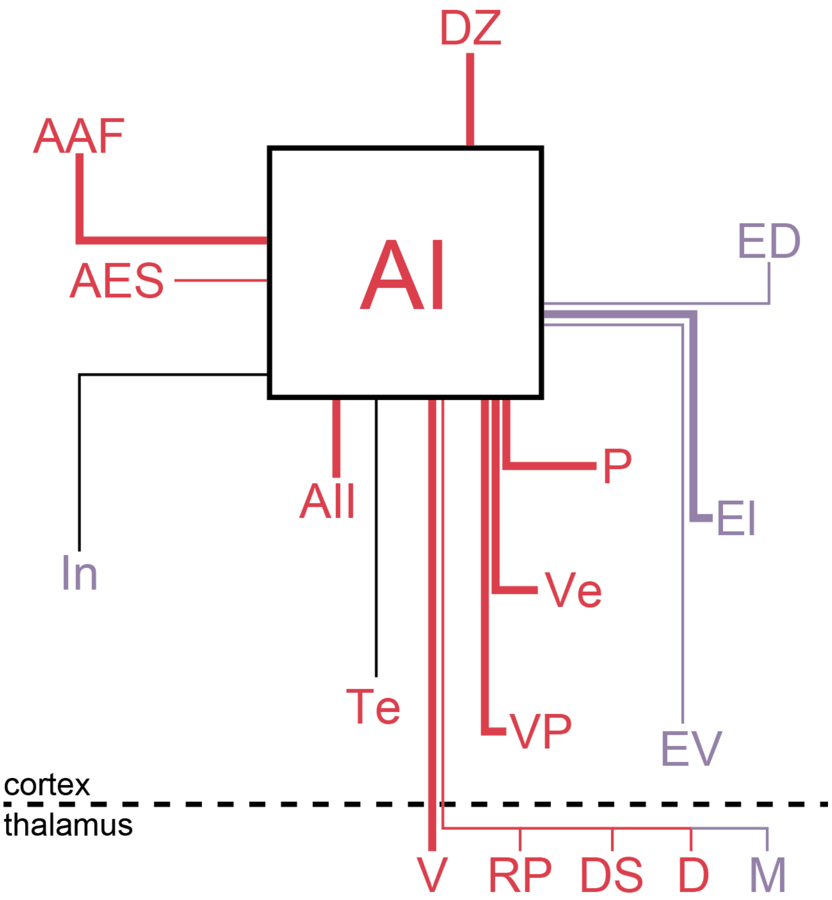


Figure 1-3: Major cortical and thalamic inputs to primary auditory cortex of the cat. For abbreviations refer to table 1. Color conventions are as follows; auditory – blue, multisensory – purple, and other – black. Abbreviations: see abbreviation list.

2. Physiology

A1 in the cat is tonotopically organized with a high to low frequency gradient going from the anterior to the posterior portion (Merzenich et al., 1975; Schreiner & Mendelson, 1990). A1 neurons are binaurally excited (Imig & Adrian, 1977; Middlebrooks et al., 1980), narrowly tuned (Schreiner & Mendelson, 1990), and their activity reflects temporal and spectral features of dynamic auditory stimuli (Atencio & Schreiner, 2010; Eggermont, 1998a; Ehret & Schreiner, 1997; Schreiner & Urbas, 1988; Schreiner et al., 2000). Furthermore, A1 neurons show a remarkable degree of plasticity based on sensory experience (Keeling et al., 2008; Kilgard et al., 2001). Generally, A1 is considered to be void of a spatial map, but some physiological and anatomical data suggest otherwise (Eggermont, 1998b; Eggermont & Mossop, 1998; Read et al., 2001). Further support stems from a series of cooling experiments implicating that A1 is critical for accurate sound localization (Malhotra & Lomber, 2006; Malhotra et al., 2004; Malhotra et al., 2008) Interestingly, although generally scarce, mapping studies demonstrate the presence of non-auditory response in A1 (Davies et al., 1954, 1956; Evans & Whitfield, 1964) with is generally supported by the presence of visual responses in the deaf cat shortly after hearing loss (Rebillard, Carlier, & Pujol, 1977; Rebillard et al., 1980; Rebillard, Carlier, Rebillard, et al., 1977) although these findings are somewhat controversial (Kral et al., 2003; Stewart & Starr, 1970).

Why should we study the cat primary auditory cortex in a multisensory context?

Despite recent evidence that primary auditory cortex in other species can be modulated by non-dominant sensory modalities (Bizley & King, 2012; Foxe & Schroeder, 2005; Ghazanfar & Schroeder, 2006; Kayser & Logothetis, 2007; Macaluso, 2006; Schroeder & Foxe, 2004; Schroeder & Foxe, 2005), a wealth of questions remain to be elucidated. These include but are not limited to questions about the impact of spatial and temporal features of multisensory cues on A1 activity, laminar similarities and differences between auditory only and multisensory stimulation, the impact of multisensory modulations in A1 on behavior and perception, and the potential benefits or drawbacks of non-dominant influences during sensory loss. Cat A1 connectivity and unisensory physiology are well known, and thus provide an exhaustive background to investigating these novel questions. Furthermore, multisensory interactions in other cortical and subcortical regions have been extensively studied in the cat and thus offer interesting comparisons and contextual information.

g. Importance of understanding multisensory neural networks: impact on behavior and perception

Identifying, characterizing, and modeling network activity in relationship to specific behavior and perceptual processes is a primary goal of neuroscience research. Much headway has been made in identifying and characterizing multisensory integration in single neurons as well as in smaller, localized neural population but extending this research to larger circuits and network processing has only just begun. Investigations into direct contributions of multisensory interactions to behavior and perception are in their infancy stages. This becomes particularly apparent with recent findings of multisensory modulations in unisensory cortices. A thorough analysis detailing processing characteristics between traditional multisensory structures and unisensory regions is crucial here and may uncover fundamental mechanistic similarities and differences of multisensory integration. Applying this knowledge to complex behavioral and cognitive processes begins to be fruitful in furthering our understanding of how our brain works and may then be extended to disorders and disease and associated therapeutic endeavors.

The current thesis sought to address a few key concepts discussed above. Experiments were targeted to explore mechanisms within which multisensory stimuli are processed across various brain structures in order to delineate common features and differences across these areas in the context of factors influencing multisensory integration. Chapter 3 and 4 discuss data from multilaminar recordings in cat insula (AS) and auditory cortex (A1) emphasizing processing involving traditional bimodal as well as modulatory integration. Chapter 5 and 6 focus on characterizing the interrelationship between the principles of multisensory integration at the level of the neuron (chapter 5) and in human performance (chapter 6). Throughout these investigations (particularly the experiments involving insula) and associated literature reviews, it became apparent that a region previously identified as a single multisensory structure (AESc) may not be a functional unit as it has been described in the past. Thus chapter 2 reviews the state of the field of cortical multisensory processing in the cat with emphasis on similarities and differences between cat AESc and insula suggesting that at least subfields of AESc are an extension of the posterior sensory portion of insular cortex.

CHAPTER II

BREAKING UP IS HARD TO DO: A REVISED VIEW OF CORTICAL PARCELLATION IN CAT ASSOCIATION CORTEX

This chapter is a review in preparation for submission to the journal 'Cerebral Cortex' as: Krueger Fister J, Sarko DK, Nidiffer AR, Meredith MA, and Wallace MT. Breaking up is hard to do: a revised view of cortical parcellation in cat association cortex.

General introduction

Our brain is continually processing information from the different sensory modalities. In order to accurately represent our world, the central nervous system must integrate and segregate this information in order to create a unified perceptual representation. In addition, having information available from multiple senses often confers marked behavioral and perceptual benefits for the organism. Extensive evidence from both animals and humans has shown that the presence of information from two or more sensory modalities can result in dramatic improvements in stimulus detection and discrimination, target localization, and the disambiguation of signals embedded in noisy backgrounds (Bremner et al., 2012; Calvert et al., 2004; *The neural bases of multisensory processes*, 2012).

The importance of these multisensory processes for adaptive behavioral, perceptual and cognitive performance is reflected in the organization of the nervous system, which has created specialized architectures for the combination and integration of information from the different sensory systems. Indeed, multisensory brain regions are found along the length of the neuroaxis from the spinal cord and brainstem to the association regions of neocortex (for a brief review see (Stein & Stanford, 2008)). Furthermore, recent work has extended our understanding of the multisensory brain to include regions classically considered unisensory or modality-specific, since increasing evidence suggest that these regions can be influenced from inputs from non-dominant modalities. Indeed, in the course of this review, we will extensively examine this issue of how we describe and think about “unisensory” and “multisensory” brain areas.

Perhaps the best-studied multisensory region to date is a midbrain structure – the superior colliculus (SC) (for review, see Stein & Meredith, 1993). Indeed, many of the operational principles of multisensory neurons were first defined in the SC (Meredith & Stein, 1983, 1986a; Meredith et al., 1987). In addition, the SC has been an excellent model for this work because of its well-defined behavioral role. Thus, several SC studies have begun to link its important role in orientation movements of the eyes, ears, head and body toward a stimulus of interest with its underlying neuronal activity (Jay & Sparks, 1987; Sparks, 1986).

Although we have learned much from studies of the SC in regards to multisensory neurons and behavior (and the relationship between them), in order to begin to understand multisensory perceptual and cognitive processes we must shift our attention to cortical regions and networks. For it is these cortical domains that are more likely to be instrumental in the creation of our unified perceptual gestalt, and in mediating the perceptual benefits (such as the improvement in speech comprehension in the presence of auditory and visual cues) that often arise from having multisensory information available.

Numerous cortical domains in a variety of species have been identified to receive convergent input from multiple senses. In monkeys and man, several of the best studied of these include regions surrounding the superior temporal sulcus (STS) and the intraparietal sulcus (e.g., areas VIP and LIP), as well as portions of orbitofrontal and prefrontal cortex (Stein & Stanford, 2008; Werner, 1993). In carnivores, most notably the cat, the best-studied cortical multisensory domain is the region surrounding the anterior ectosylvian sulcus (AES). Given the wealth of information derived from this region as it relates to both sensory-specific and multisensory function, the current review will focus on the cat AESc (i.e., the cortex surrounding the AES) as a model for understanding the anatomy and physiology of multisensory cortical regions. In addition, a strong emphasis will be placed on comparing and contrasting AESc to surrounding cortical regions in an effort to differentiate distinctions that are unique to multisensory cortices. Within such a framework, we will re-examine arguments concerning the unisensory (i.e., modality-specific) and multisensory character of the AESc, as well as whether this cortical domain should be considered as a single functional unit and will identify properties that extrapolate to other cortical areas that, as such, may represent features common to multisensory cortices in general.

Multisensory Nomenclature

Before embarking on an analysis of the sensory and multisensory properties of the AESc, it is important to establish definitions for essential terms. Some of these issues have already been addressed (Stein et al., 2010), but require explicit reiteration here. Although the concept of multisensory processing is an old one, neurons identified as multisensory were first reported in the 1960's (e.g., (Horn & Hill, 1966)). These neurons were activated (i.e., generated action potentials) by stimuli from more than one sensory modality, and were described as “bimodal” (e.g., activated by visual and by auditory cues, see also Figure 2-2a) or “trimodal” (e.g., activated by visual, auditory and somatosensory cues). A more encompassing and intuitive term, that avoids eponymous confusion, for neurons that show such frank responses to stimuli from multiple sensory modalities, is that of an “overt” (see also Figure 2-2b) neuron, which will be used here. Several decades later, neurons were identified in which spiking could only be generated from a single modality, but in which these spiking responses could be significantly modulated by stimuli from a different sensory modality. These neurons meet the contemporary definition for being multisensory (i.e., they could be influenced by stimulation in more than one sensory modality). It is important to point out that these neurons failed to meet the definition of “bimodal” or “trimodal,” and were not overtly multisensory, yet they cannot and should not be labeled as “unisensory.” Such neurons, first identified in the AESc, were labeled as “subthreshold” multisensory neurons (Dehner et al., 2004), being overtly activated by stimuli from one sensory modality but their activity was significantly influenced by the presence of a cue from an otherwise apparently ineffective modality. Within a few years, neurons showing similar subthreshold characteristics were identified in the various divisions of AESc as well as in a number of other cortical regions (FAES, (Meredith & Allman, 2009; Meredith et al., 2006); PLLS, (Allman & Meredith, 2007; Clemo et al., 2008); RSS, (Clemo et al., 2007); AEV, (Wallace et al., 2006); ferret RSS, (Keniston et al., 2009); ferret A1/AAF, (Bizley & King, 2008; Meredith et al., 2012); ferret PPr, (Foxworthy et al., 2013)). These neurons were demonstrated to exhibit responses that were sensitive to changes in the quality of stimulation (e.g., were not simply an alerting/distracting effect; (Allman, Bittencourt-Navarrete, et al., 2008)) and have been postulated to represent a form of multisensory neuron that provides a connectional continuum between purely unisensory and overtly multisensory neurons that ultimately accounts for the broad range of multisensory processing (for review, see (Allman et al., 2009)). In recent years, a more intuitive term describing these subthreshold influences has been introduced: “modulatory” multisensory neurons, which will be used here (Sarko et al., 2012; Stevenson, Ghose, et al., 2014). For any multisensory processing to occur, synaptic inputs from different sensory modalities must meet on the same neuronal membrane and this connectional feature is defined as multisensory convergence. This anatomical property is the necessary prerequisite for the physiological processing that ensues. Last, the terms multisensory and crossmodal are not used as synonyms here, since the previous indicates the influence of more than one sensory modality while “crossmodal” indicates the crossing of one sensory modality (i.e., unisensory) into another (i.e. also unisensory).

It is important to understand that although anatomical convergence of inputs from different sensory modalities produces a multisensory neuron (as defined above), it is the resulting spiking activity that actually represents multisensory processing. Numerous techniques have been proposed by which multisensory processing is measured, but the method used first by Meredith & Stein (Meredith & Stein, 1983) has been employed by many subsequent studies of multisensory neurons (see for review (Stein et al., 2009; Stevenson, Ghose, et al., 2014)). In these investigations, multisensory integration was observed if the spike counts of neuronal responses to combined (multisensory) stimulation significantly changed from the response to the most effective individual stimulus (unisensory), where increased multisensory responses were indicative of response enhancement and decreased multisensory responses represent multisensory depression. These integrative effects are not random, but are governed by the location, relative timing and effectiveness of the stimuli. Thus, a given neuron can show a range of different multisensory integrative effects (Meredith & Stein, 1986a; Meredith et al., 1987; Perrault et al., 2005). Other measures have also been utilized to assess neuronal multisensory integration, such as proportional measures (superadditivity, subadditivity, etc;(Laurienti et al., 2005; Stein et al., 2009; Stevenson, Ghose, et al., 2014)) and Information Theoretic (Bizley & King, 2009), but will not be emphasized in this review.

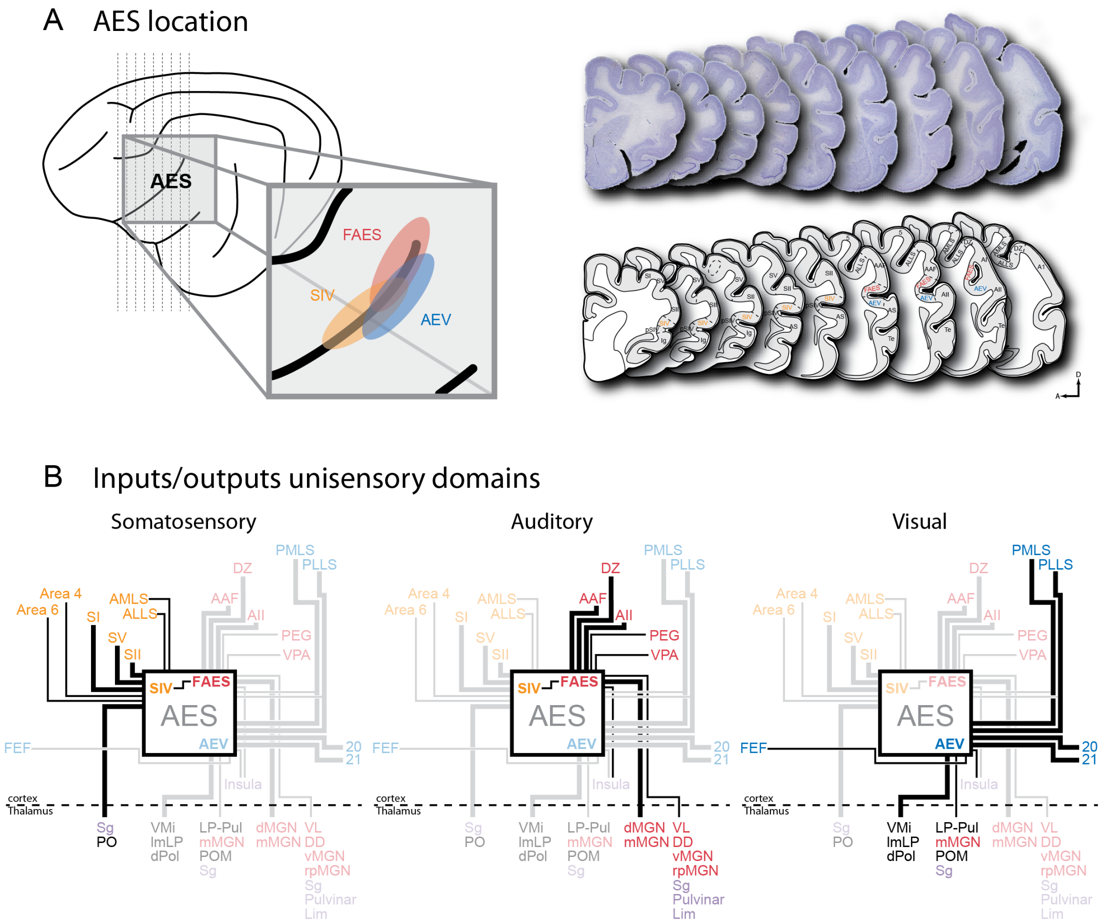


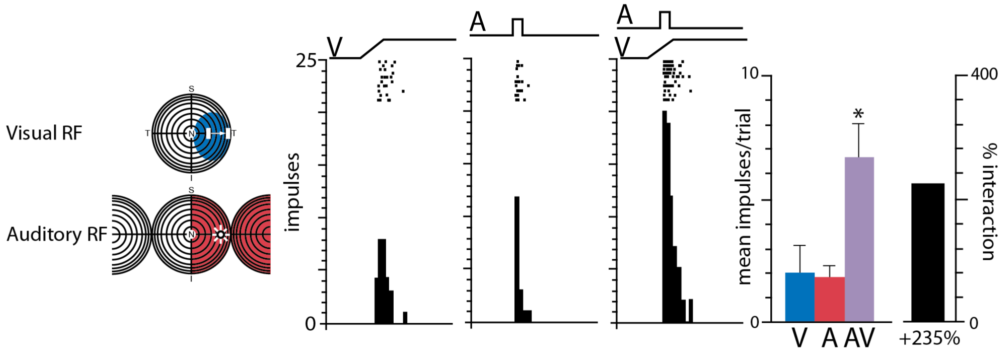
Figure 2-1: **A** (left) – Location of anterior ectosylvian sulcus (AES) in the cat. **A**(right) – Consecutive sections with Nissl stain and reconstructed sections (anterior – right to posterior – left) depicting the location and extend of AES subregions. **B** – Major inputs to the three unisensory domains of AESc. Color conventions are as follows; somatosensory – orange, visual – blue, auditory – red, multisensory – purple, and other - black.

A brief introduction to AESc

AES is located at the junction between the frontal, parietal and temporal divisions of cat cerebral cortex. The region is made up of the tissue on both banks as well as within the fundus of the AES, and historically has been divided into three distinct zones, each of which is dominated by responses to a different sensory modality: the fourth somatosensory cortex (SIV), the anterior ectosylvian visual area (AEV), and the auditory Field AES (FAES). As depicted in Figure 2-1, area SIV, situated in the anterior and dorsal regions of the AESc, contains a full somatotopic representation of the body (Clemo & Stein, 1983). Ventral to SIV, deep within the sulcus, is a small non-somatotopic zone referred to as para-SIV (Clemo & Stein, 1983), which then transitions into AEV (Mucke et al., 1982; Olson & Graybiel, 1987). AEV is particularly responsive to moving visual stimuli (Benedek et al., 1988). The posterior dorsal pole of AES is occupied by FAES, a non-tonotopic field that includes neurons tuned for acoustic spatial features (Clarey & Irvine, 1990b; Middlebrooks et al., 1994).

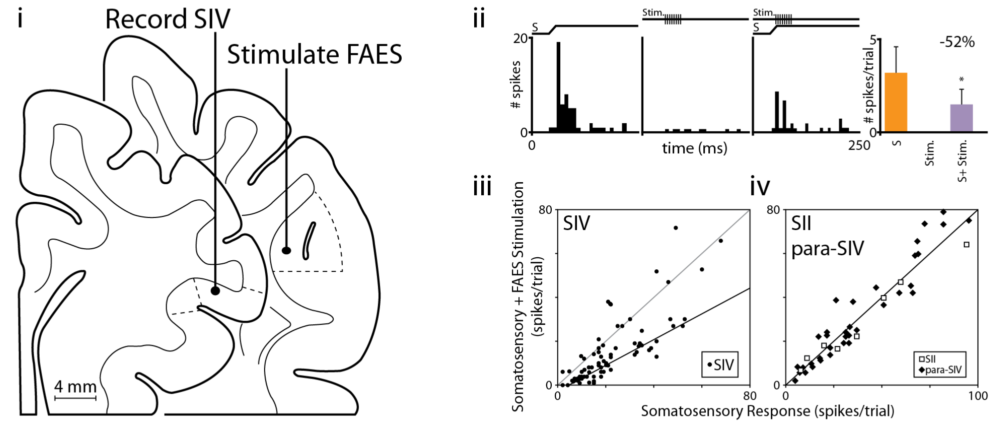
In addition to these so-called ‘unisensory’ divisions of AESc, multisensory neurons are found to be plentiful, and include neurons that are overtly multisensory (Carriere et al., 2008; Wallace et al., 1992), as well as those characterized as modulatory (Carriere et al., 2008; Dehner et al., 2004; Meredith & Allman, 2009). Distributionally, whereas overt multisensory neurons are largely concentrated in the borders between the major AESc subdivisions, modulatory neurons (as well as unisensory neurons) appear to be more common within the major fields of AESc (Calvert et al., 2004; Stein, 2012; Wallace et al., 1992). In the following sections, we describe each of these AESc divisions in greater detail, with an emphasis on the anatomy, physiology and functional relevance of these areas and their constituent neurons. After that, the distribution of multisensory properties within and between the different zones will be discussed.

A Frank Multisensory Interactions



B Modulatory Multisensory Interactions

somatosensory-auditory interactions



auditory-visual interactions

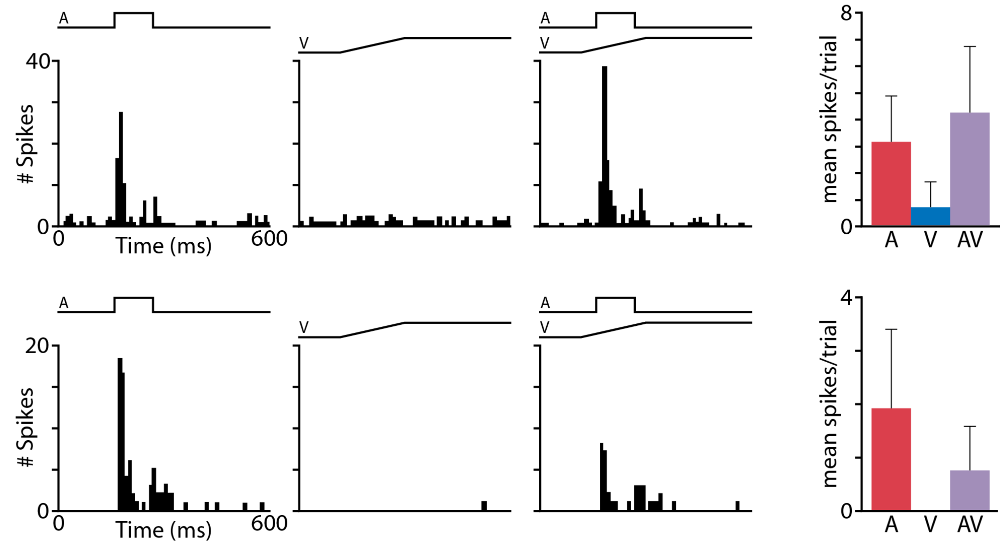


Figure 2-2: **A** – Example of traditional bimodal integration. **B** – Examples of modulatory multisensory interactions. Color conventions are as follows; somatosensory – orange, visual – blue, auditory – red, and multisensory – purple.

The unisensory domains of AESc

The somatosensory AES: fourth somatosensory area

1. General location and characteristics of SIV

The fourth somatosensory area (SIV, (Clemo & Stein, 1982, 1983)) occupies the lower ¼ of the anterior ectosylvian gyrus (lateral to the SII body map) and crosses the lip of the sulcus to occupy the dorsal bank of the AES. In SIV the layer 4 is narrow and sublamination is not apparent; layers 2/3 and 6 are largely populated by small/medium-sized pyramidal neurons while a band of large pyramidal neurons cytoarchitectonically characterizes this region (Clemo & Stein, 1983). Although the chemoarchitecture of this region has not been reported, inhibitory, GABAergic interneurons are found across all laminae, but peak in concentration in layers 1/2, corresponding with the distribution of Calbindin- and Calretinin-positive subtypes. In contrast, few Parvalbumin-positive interneurons are found in layer 1/2 locations, but predominate at layer 3/4 levels (Clemo et al., 2003).

2. Anatomical connections of SIV

The major anatomical inputs to SIV originate from ipsilateral somatosensory cortical areas SII, SV and contralateral SIV as well as from suprageniculate (Sg) and posterior (PO) thalamic regions (Burton & Kopf, 1984; McHaffie et al., 1988; Reinoso-Suarez & Roda, 1985). Outputs from SIV have not been as extensively examined, but include those to the somatosensory region SV (Clemo & Meredith, 2004), and to the FAES (Burton & Kopf, 1984; Dehner et al., 2004; Reinoso-Suarez & Roda, 1985) The best characterized projections of SIV are those that target a midbrain structure and terminate in the deep layers of the superior colliculus (SC, (Clemo & Stein, 1984, 1986;

McHaffie et al., 1988; Wallace et al., 1992)). This corticotectal projection is topographic (Clemo & Stein, 1984) and provides a heavy source of drive to the deep SC, as shown by the substantial reduction in somatosensory activity in the deep SC during SIV deactivation (Clemo & Stein, 1986).

3. Physiology of somatosensory responses in SIV

Activity in SIV usually consists of short bursts (1-4) of spikes and is overwhelmingly driven by hair receptors on the contralateral body surface with only rare instances of inputs from skin and deep receptors. Some of the basic physiological measures of SIV responses are detailed and compared in Table 1. The receptive fields of SIV neurons are somatotopically organized such that the head is represented anteriorly and the tail/hindlimb regions posteriorly. The forepaw and hindpaw representations extend dorsally onto the lip of the AES (where receptive fields reverse to become part of the SII representation on the anterior ectosylvian gyrus (Burton et al., 1982; Clemo & Stein, 1982), while the trunk and dorsal aspects of the body are located inferiorly (ventrally), deep within the wall of the sulcus. In comparison to receptive fields in the primary somatosensory area (S1), those of SIV neurons are consistently larger and generally include multiple vibrissae or multiple digits, or extend across a joint to include forelimb, elbow and shoulder, or hindpaw, knee and hip regions (Clemo & Stein, 1983). Given their size, response heterogeneity across the dimensions of the receptive field is common and can be characterized by a central area of best activity (Clemo and Stein, 1983). Deep to SIV in the dorsal bank and extending through the fundus of the AES lies a separate, less examined somatosensory region designated para-SIV (Clemo & Stein, 1983, 1984). Para-SIV lacks a demonstrable somatotopic organization, perhaps because neurons here have very large receptive fields that are often bilateral, encompass the whole body surface, or represent discontinuous segments of the body. The response properties of para-SIV neurons, many of which show overtly multisensory effects (largely somatosensory-visual; Clemo and Stein, 1983), have not been extensively examined.

4. Multisensory features of SIV

Numerous recording studies of SIV have described the somatosensory nature of neuronal responses there, while overt (e.g., bimodal) multisensory neurons have rarely been encountered within the core of SIV (Clemo & Stein, 1982, 1983, 1984; Jiang et al., 1994b). Despite the lack of evidence for overt multisensory neurons in SIV, figures depicted in several anatomical studies (Burton & Kopf, 1984; Reinoso-Suarez & Roda, 1985) suggested connectivity between SIV and the adjacent auditory FAES. In fact, Dehner et al. (Dehner et al., 2004) demonstrated a robust crossmodal projection originating largely from pyramidal neurons in layers 2/3 of FAES that terminated primarily in the supragranular layers of SIV. Because pyramidal neurons are largely glutamatergic, this crossmodal projection would be expected to be excitatory, and thus overt auditory responses should be present in SIV. However, experiments again failed to demonstrate the presence of overt auditory or audio-tactile responses in SIV. However, the use of *combined* tactile and auditory stimulation (Figure 2-2b) revealed a significant cross modal suppression of tactile responses in the many SIV neurons (Dehner et al., 2004). Mechanistically, it was suggested that these influences were mediated by inhibitory interneurons, which reversed the excitatory drive from FAES (Clemo et al., 2003). To test this possibility, the responses of SIV neurons were tested during the administration of the GABA antagonist, bicuculline methiodide, which blocked the suppressive effect of auditory stimulation on somatosensory responses in SIV. Such "subthreshold" influences, now considered under the rubric "modulatory," have already been described in a variety of other neural structures and species (Allman & Meredith, 2007; Allman, Keniston, et al., 2008; Allman, Bittencourt-Navarrete, et al., 2008; Barraclough et al., 2005; Bizley et al., 2007; Carriere et al., 2007; Clemo et al., 2007; Meredith & Allman, 2009; Meredith et al., 2006; Newman & Hartline, 1981; Sugihara et al., 2006). Furthermore, the anatomical correlates of these modulatory multisensory influences have now been documented where projections from FAES have been shown to terminate on interneurons in SIV (Keniston et al., 2010).

The collective results of this work have detailed the presence of substantial multisensory influences in the core of SIV, with these influences coming largely from adjacent auditory region of AESc (i.e., FAES) and being modulatory in character. The functional relevance of these findings remains to be fully elucidated, but suggest that the transformations taking place within SIV (and consequently the outputs of this region) are not purely somatosensory in nature but are likely to reflect multisensory influences on tactile processing and function.

5. Possible functional roles of SIV

Given its strong and well-documented relationship to the SC, it has been proposed that area SIV plays an important role in controlling or modifying orienting behaviors to somatosensory stimulation (Clemo and Stein, 1986). Not only does SIV project directly to the deep layers of the SC, but SIV also has an indirect connection to the SC through the FAES that, by suppressing FAES activity and its effects on the SC, could facilitate somatosensory target selection in the SC (Meredith et al., 2006). Consistent with this notion, a preliminary study in awake cats showed that focal stimulation primarily within this region of the AES elicited coordinated gaze shifts and contralateral reaching movements of the forepaw (Cullen et al., 1993; Jiang et al., 2002).

Visual AES: the AEV

1. General location and characteristics of AEV

The caudal two-thirds of the ventral bank of AES, known primarily as AEV (alternatively referred to as AESv or the ectosylvian visual area, EVA, in some studies; e.g., (Olson & Graybiel, 1987)), constitutes the visual subdivision of AES due to its principal cortical connections with extra primary visual areas and areas surrounding the suprasylvian sulcus (Grant & Shipp, 1991; Miceli et al., 1985; Mucke et al., 1982; Nakai et al., 1987; Norita et al., 1986; Olson & Graybiel, 1987; Reinoso-Suarez & Roda, 1985; Squatrito et al., 1981).

Like its counterparts in the AESc, the AEV is characterized by a compressed layer 4, while its supragranular layers are comparatively expanded. Cytoarchitectonic features identified using neurofilament staining (SMI-32) reveal densely stained neuronal profiles and neuropil particularly within layer 3 that is substantially reduces in layers 5/6 (van der Gucht et al., 2001). Whereas cortical lamina IV is well developed and a hallmark feature of primary sensory areas, it is reduced in secondary sensory areas and is minimally present across the subdivisions of AES. Beyond a diminished layer IV, Nissl-stained sections characterize AEV with the presence of scattered clusters of one to five large pyramidal cells in layer V, in addition to a thin layer VI characterized by cell bodies arranged in column-like aggregates (Clasca et al., 1997). Layers IIIa and IIIb are distinguishable although the supragranular layers are thin overall. Myelin staining also revealed dense radial and horizontal fibers extending from the white matter to layer II (Clasca et al., 1997). Acetylcholinesterase-positive neuropil is scarce except in layer I, but many of the large pyramidal cells in layer V stain densely with ACh and cytochrome oxidase (Clasca et al., 1997).

Using the SMI-32 monoclonal antibody to label the soma and dendrites of pyramidal cells in layers III, V, and VI, van der Gucht et al. (van der Gucht et al., 2001) further characterized AEV and demonstrated layers III and V to contain many SMI-32-positive pyramidal neurons with apical dendrites and darkly stained perikarya. Whereas layer V had sparsely distributed darkly stained neurons, layer III consisted of mostly smaller pyramidal neurons that were more densely packed in layer IIIb. Layer IIIa contained a dense distribution of darkly stained SMI-32 apical dendrites arising from the pyramidal neurons in IIIb, and layer VI exhibited weak neuropil staining with a low density of labeled fibers. In a separate study, neurons responsive to audiovisual stimulus combinations were also labeled with biocytin and determined to be predominantly pyramidal cells in layers V and VI (Kimura et al., 1996).

Because a balance of inhibition shapes sensory receptive fields and neuronal response properties, and differential distribution of interneuron subtypes suggests differential involvement in neural circuitry, Clemo et al. sought to characterize the distribution of GABA-ergic neurons (and their co-localized calcium binding proteins including calbindin, calretinin, and parvalbumin) for each subdivision of AES (Clemo et al., 2003). They found that GABA-ergic neurons were located in laminae I-VI but particularly concentrated in laminae II-III. Calbindin-positive neurons were concentrated in laminae II-III as well, but with little representation in any other laminae. Calretinin-positive neurons were concentrated within supragranular layers I-III but declined sharply in IV-VI. Parvalbumin-positive neurons showed highest concentrations in the granular layer.

2. Anatomical connections of AEV:

Inputs

The principal cortical connections of AEV are with extrastriate visual areas 20 and 21 in addition to visual areas surrounding the suprasylvian sulcus (particularly the posteromedial lateral suprasylvian visual area, (Grant & Shipp, 1991; Miceli et al., 1985; Mucke et al., 1982; Nakai et al., 1987; Norita et al., 1986; Olson & Graybiel, 1987; Reinoso-Suarez & Roda, 1985; Squatrito et al., 1981)). Cortical input to AEV is densest from lateral suprasylvian visual areas (Olson & Graybiel, 1987). Extensive projections were also seen to AEV from VM, the lateromedial subdivision of LP, and dorsal PoI, whereas moderate inputs from PoM, the suprageniculate nucleus (Sg), and the magnocellular division of MGN were observed (Minciacchi et al., 1986; Norita et al., 1986; Olson & Graybiel, 1987; Roda & Reinoso-Suarez, 1983).

Outputs

Ventral AEV was found to project to all ipsilateral frontal oculomotor areas in the cat, including the medial wall of the hemisphere under the cruciate sulcus (which controls contralateral conjugate eye deviation), the fundus of the coronal sulcus (which controls monocular movement of the contralateral eye), and both medial and lateral banks of the presylvian sulcus (influencing conjugate eye deviation and centering eye movement, respectively) (Guitton & Mandl, 1978a; Hassler, 1966; Nakai et al., 1987; Schlag & Schlag-Rey, 1970). AEV also projects heavily and bilaterally to the deep layers of the superior colliculus, which in turn mediate orientation movements of the head and eyes (Casagrande et al., 1972; Segal & Beckstead, 1989; Tortelly et al., 1980). Efferents from AEV to the thalamus connect ipsilaterally to VM (particularly the rostral extent), presumably facilitating sensorimotor integration, and ipsilaterally to the lateromedial division of LP as well as the LM-Sg complex (Norita et al., 1986; Olson & Graybiel, 1987). Furthermore, caudate, putamen, lateral amygdala, and pontine nuclei, all receive inputs from AEV (Fuentes-Santamaria et al., 2009; Miyashita & Tamai, 1990; Nagy et al., 2011; Norita et al., 1986).

3. Physiology of visual responses in AEV

Visual responsiveness of AEV was confirmed through electrophysiological studies (Mucke et al., 1982; Olson & Graybiel, 1983), and some of the basic physiological measures of AEV responses are listed in Table 1. Neurons of AEV had strong preference for small (1° x 1°), rapidly moving spots of light within a large receptive field and with strong directional specificity (Benedek et al., 1988; Mucke et al., 1982; Olson & Graybiel, 1983, 1987; Scannell et al., 1996). These preferences were similar to that of insular cortex in the cat, with the exceptions that insular cortex preferred lower stimulus velocities and larger stimuli overall (Benedek et al., 1986; Benedek et al., 1996). It was also discovered that AEV is attuned to detection of pattern motion such as the direction of drifting gratings (Nagy et al., 2003) or plaid patterns made by superimposing two differently oriented gratings (Scannell et al., 1996). Encoding of such complex feature selectivity is indicative of higher-order motion processing areas such as primate area MT (e.g., (Movshon et al., 1985; Rodman & Albright, 1989). Despite the large receptive field size characterizing AEV, its neurons retain a robust capacity for spatial localization of stimuli (Benedek et al., 2000). The highest firing rate could be elicited by a “best area,” and although surrounding regions continued to elicit a high firing rate, the strength of the response decreased with increasing distance from the best area, thus providing a mechanism for subregions of a receptive field to be encoded through graded firing rate outputs (Benedek et al., 2000). The areas producing maximal firing rates predominantly centered on the area centralis, a finding that complements the spatial tuning properties of FAES neurons (Benedek et al., 2000; Middlebrooks et al., 1994; Middlebrooks et al., 1998).

4. Multisensory features of AEV

To date, AEV neurons have not been explicitly tested for modulatory interactions with other sensory modalities.

5. Possible functional roles of AEV

To date, AEV has most often been implicated on being an integral part of a gaze motor loop. Yet, studies have found opposing results. One set of studies showed that neurons in AEV discharge just prior to saccades (Tamai & Kimura, 1996; Tamai et al., 1989), and the majority of AEV neurons that were shown to be directionally selective in response to gratings preferred motion toward the midline rather than away from it (Scannell et al., 1996). Indeed, stimulation of deep layers of AEV (using a brief current of approximately 33 μA) was found to elicit centering eye movements in anesthetized animals (Tamai et al., 1989). These evoked saccadic eye movements persisted even after bilateral ablation of FEF, implicating a role for AES in controlling eye movements, likely through projections to SC (Tamai & Miyashita, 1989; Tamai et al., 1989). One major criticism that these studies received is that elicitation of centering eye gazes would be contraindicated for an AEV connection to the SC, which produces conjugate collateral saccades.

A second set of studies also implicates AEV's role in orientation behaviors. Given the extensive projections from AES to SC, and the potential for AES to ultimately influencing outputs from the SC via the tecto-reticulo-spinal tract controlling orientation behaviors, Wallace et al. sought to elucidate connectivity between the two regions (Wallace et al., 1993). They discovered that unisensory zones of AES produced convergent inputs on multisensory neurons of the SC (e.g., AEV and FAES converging on an audiovisual neuron of the SC) and that these SC neurons in turn formed the principal component of the tecto-reticulo-spinal tract. Also, despite the lack of retinotopic organization in AEV, when AEV neurons were stimulated and subsequently activated SC neurons, the receptive fields of each corresponded well, indicating that general principles of mapping visual space were preserved (Wallace et al., 1992).

However, despite stimulation experiments implicating a role in gaze direction to visual targets (Tamai & Miyashita, 1989; Tamai et al., 1989), cooling experiments targeting the AEV with reversible deactivation failed to impact the animal's ability to redirect gaze (Lomber & Payne, 2004). These observations would seem to reinforce the notion proposed by Scannell et al. (Scannell et al., 1996) that the principal role of the AEV is involved in motion perception and discrimination. These authors proposed that because AEV appears to synthesize information about the same direction of motion from different regions of visual space, it is poised for involvement (Scannell et al., 1996). Ultimately this would facilitate behaviors that are crucial for survival such as navigating the environment, tracking prey, and detecting threats. Indeed, in addition to registering external motion (Scannell et al., 1996) or self-generated motion, it was proposed that AEV utilizes these connections to functionally relate visual inputs to limbic system activity, potentially driving orientation and alertness behaviors and directing visual attention (Norita et al., 1986).

Auditory field of the AES: the FAES.

1. General location and characteristics of FAES

Auditory field AES (FAES) is located within the dorsal posterior portion of AES being situated posterior to the fourth somatosensory area (SIV) and dorsal to anterior ectosylvian visual area (AEV). The physical location of FAES, immediately adjacent to the anterior auditory field (AAF), and subjacent (in sulcal wall deep) to primary and secondary auditory cortex, and its physiological response properties make it not just part of AES but also part of the belt of auditory association cortices.

Much of the FAES lies submerged deep to the middle ectosylvian gyrus where it surrounds the posterior remnant of the sulcus on its medial, dorsal and lateral aspects like an inverted “U” shape. The more anterior portions of the FAES are apparent in the dorsal bank of the AES as it emerges from its position deep to the middle ectosylvian gyrus and this portion shares a border with the antero-ventral aspects of the AAF. The cortical mantle occupied by the FAES is considerably compressed and routine Nissl stains often reveal a lightly stained layer 1, well stained layers 2/3 and 5/6 separated by a very narrow, unstained band representing layer 4. Cytoarchitectonic features revealed through neurofilament staining (SMI-32) show moderate immunoreactivity of neuronal profiles in layers 2, 3 and 5 that is somewhat lighter in layer 6 (Mellott et al., 2010). Subtle differences in these labeling patterns have been reported between the medial and lateral aspects of the FAES. Moderate levels of AChE staining have also been described in layers 3, 4, and 6 (Wallace et al., 1991). Like the corresponding regions of the AES, the distribution of GABAergic interneurons spans all cortical layers, but is biased toward layers 1/2, where Calbindin- and Calretinin-positive subtypes also preferentially occur. In contrast, Parvalbumin-positive interneurons tend to avoid layers 1/2, but are most prevalent at the lower levels of 3/4 (Clemo et al., 2003).

2. Anatomical connections of FAES

Inputs

Studies placing retrograde anatomical tracers into FAES showed that auditory inputs primarily arise from the dorsal zone (DZ) and the anterior auditory field (AAF) of auditory cortex as well as the dorsal and magnocellular divisions of the medial geniculate nucleus in auditory thalamus (dMGN and mMGN, respectively) (Lee & Winer, 2008c; Meredith & Clemo, 1989). Less robust cortical projections originate in the secondary auditory cortex (AII) and the posterior auditory cortex such as the ventral posterior auditory area (VPA), insula (In), and the dorsal and intermediate posterior ectosylvian gyrus (PEG; (Lee & Winer, 2008a); see also chapter 21 by Meredith 2004 in *The Handbook of Multisensory Processes)*). Additionally, weak projections from other subregions of auditory thalamus such as the ventral division (vMGN), the deep dorsal nucleus (DD), the ventrolateral nucleus (VL), and the rostral pole of MGN have also been identified (Lee & Winer, 2008c). Using vesicular glutamate transporter 2 (VGlut2) immunohistochemistry, which is a marker for thalamocortical terminals, Hackett and colleagues (2013) showed preferential distributions within layers 3b/4 and 1a of the FAES, but sparse labeling in layer 6, which is the common pattern of thalamic inputs across association cortices.

Non-auditory inputs to the FAES have also been reported to arise from the ventral bank of the suprasylvian sulcus (corresponding with PMLS/PLLS visual regions), insular cortex, posterior rhinal sulcus, as well as somatosensory regions SIV and para-SIV ((Clarey & Irvine, 1990a; Reinoso-Suarez & Roda, 1985), Thalamic inputs to the FAES include the suprageniculate nucleus (Sg), the posterior nuclear group, the pulvinar complex, and the principle division of the ventromedial nucleus (Clarey & Irvine, 1990a; Roda & Reinoso-Suarez, 1983). Interestingly, a study by Meredith et al looking at AES intrinsic connections did not find connections from AEV to FAES (Meredith (2004)), despite that they share a common border. Interhemispheric (callosal) connections to FAES arise from contralateral AES (no specific sensory domain indicated) and the suprasylvian sulcus (Clarey & Irvine, 1990a).

Outputs

Like its counterparts in the AESc, perhaps the best studied output target of the FAES is the superior colliculus, specifically its intermediate and deep (multisensory) layers (Chabot et al., 2013; Fuentes-Santamaria et al., 2008; Meredith & Clemo, 1989) FAES projections to auditory cortical areas include primarily DZ, AII and In (Lee & Winer, 2008a), while non-auditory projection targets include somatosensory area SIV (Dehner et al., 2004; Keniston et al., 2010) , insula (Lee & Winer, 2008a), the multisensory zone of the AEG (MZ) and rostral suprasylvian sulcal cortex (RSSc; (Clemo et al., 2007; Monteiro et al., 2003) and visual PLLS (Clemo et al., 2008), the motor cortex and pontine nuclei (Gimenez-Amaya, 1988).

3. Physiology of auditory responses in FAES

Unlike the well-known tonotopically arrangement of its cortical neighbors AAF and A1, no such organization has been identified for the FAES and FAES neurons have been reported to respond best to broadband noise. That said, FAES neurons do respond to pure tones, exhibit broad tuning curves (Clarey & Irvine, 1990b) and even exhibit a differential distribution to frequency sensitivity (Kim et al., 2012). The majority of FAES neurons demonstrated binaural excitation, where neurons were excited by monaural stimulation of either ear (Clarey & Irvine, 1990b), which is a characteristic of omnidirectional spatial tuning. Subsequent studies also observed a dominance of omnidirectional binaural properties (Meredith and Clemo 1989, Jiang, Lepore et al. 2000). When tested for spatial tuning acuity, FAES neurons have been reported as varying from fairly narrow (Korte & Rauschecker, 1993) to broad (Jiang et al., 2000; Middlebrooks et al., 1994; Middlebrooks et al., 1998). In addition, while neurons within the posterior portion of FAES tend to exhibit a narrow spatial tuning with a strong preference for the central space, neurons within anterior FAES are broader spatially tuned, hinting that FAES may have a role in selective spatial processing (Kim et al., 2012). In addition, nearly all FAES neurons exhibit directional preferences to sound movement (Jiang et al., 2000). The basic physiological measures of auditory FAES responses are listed and compared in Table 1.

4. Multisensory features of FAES

Auditory neurons within the FAES can also be influenced by non-auditory stimulation, such as visual or somatosensory cues (Figure 2-2b). FAES is composed of a mixed population of unisensory auditory neurons (~65%), overt multisensory neurons (17%) and modulatory multisensory neurons (14%) with the vast majority (95%), of course, exhibiting auditory responses (Meredith & Allman, 2009), although another study observed that 29% of FAES neurons were also modulated by somatosensory stimulation (Meredith et al., 2006).

For FAES neurons modulated by non-auditory cues, the predominant multisensory processing effect was modality dependent, where auditory responses were significantly facilitated by visual cues (72% of modulatory neurons; (Meredith & Allman, 2009)), but were significantly suppressed by somatosensory cues (79% of modulatory neurons; (Meredith et al., 2006)). On the other hand, the overall effect of multisensory stimulation in the overtly multisensory FAES was enhancement (average= 34%; Meredith, Allman et al., 2011). As with the other subdivisions of the AESc, there appears to be a differential distribution within their respective boundaries of the different forms of multisensory neurons, which will be discussed in detail below (see Multisensory Border Regions).

5. Possible functional roles of FAES

In addition to mediating multisensory processing in SC, FAES has also been identified to play a crucial role in sound localization. A set of studies by the Lomber laboratory has investigated the role of FAES (and other regions of cat auditory cortex) in orientation behaviors to sound. Cooling (or lesioning) FAES for example results in almost complete abolishment of contralateral (to the cooling site) sound localization while no deficits were observed in orientation to visual cues (Malhotra et al., 2004; Strominger, 1969a, 1969b). A follow-up study also showed that bilateral FAES deactivation results in deficits in both hemifields (Lomber et al., 2007) Furthermore, cooling of FAES in conjunction with cooling of the primary auditory cortex (A1) or a second primary field, the dorsal zone (DZ) led to the same localization deficits as bilateral FAES deactivation. This suggests that all three areas are crucial for proper orientation to sound.

The multisensory border regions

As mentioned earlier, a majority of the frank multisensory/bimodal neurons are located within the respective borders of the three unisensory zones (Wallace et al., 1992; Wallace et al., 2006). To date, only a handful of studies have looked at their physiological properties. Findings suggest that these multisensory neurons observe the three principles of multisensory integration in that they show multisensory enhancement most often when stimuli are temporally and spatially coincident while weakly effective on their own (Wallace et al., 1992). However, recent data also indicate that these working principles are interdependent in that space and time can influence stimulus effectiveness. This becomes especially apparent when looking at their receptive field architectural features. Unisensory and multisensory RFs were both found to be greatly heterogeneous and when various spatial locations within the RFs were tested for multisensory responsiveness, greatest enhancements were observed in locations that were weakly effective during unisensory stimulation alone (Carriere et al., 2008; Royal et al., 2009). Moreover, unique temporal patterns of the response profiles were observed in that early and late response epochs had diverse multisensory integration profiles and often discharge latencies and durations differed greatly from but were dependent on the constituent unisensory responses (Royal et al., 2009).

AESc and crossmodal plasticity

Our long cultural history of blind poets and musicians has provided compelling anecdotal examples of the compensatory effects of the loss of a sensory system early in development. In fact, numerous perceptual studies have demonstrated that early blind individuals exhibit supranormal hearing abilities, similar to the supranormal visual performance of the early deaf. This substitution of one sensory modality for the loss of another is referred to as "crossmodal plasticity." However, the neural bases of crossmodal plasticity have remained largely unexamined until recently, where the AESc has played a central role. That crossmodal plasticity could be experimentally induced through sensory deprivation was revealed by the seminal studies of the AESc by Rauschecker and Korte. Adult cats visually deprived from birth (bilateral lid suture) showed enhanced auditory localization behavior (Rauschecker & Kniepert, 1994) and neuronal recordings from their AEV revealed the presence of auditory-responsive neurons where visual activation had prevailed in normally sighted animals (Rauschecker & Korte, 1993). The visually responsive neurons that remained were bimodal (i.e., also responded to either auditory or somatosensory stimuli), suggesting that AEV was functionally taken over predominantly by surrounding auditory regions of cortex (Rauschecker & Korte, 1993). Furthermore, the auditory neurons of the animals showed significantly sharper auditory spatial tuning than they did their normally-sighted counterparts (Rauschecker & Korte, 1993), which was consistent with their enhanced auditory behavioral performance (Rauschecker & Kniepert, 1994). Thus, this groundbreaking series of studies of the AESc showed that crossmodal plasticity resulted in the specific reorganization of cortical function by an intact sensory system. The effects of crossmodal plasticity following early sensory loss have also been examined in the auditory FAES, where the neurons of early-deafened cats are predominantly activated not by auditory cues, but by visual stimulation (Meredith et al., 2011). These FAES neurons of early-deaf animals exhibited response features characteristic of higher-order visual neurons, such as large receptive field size, and velocity and movement directional preferences. Furthermore, cooling deactivation of FAES resulted in the loss of detection and orientation to visual cues in early-deafened animals but not in the hearing controls (Meredith et al., 2011). Curiously, the inputs to the FAES of early-deaf animals are largely the same auditory cortical and thalamic regions that access the area in hearing animals (see above), indicating that crossmodal plasticity does not induce new sources of neuronal connections (Meredith et al., 2013). In addition, inputs from non-auditory sources (e.g., visual cortical areas) preferentially target the supragranular layers of the FAES. In correspondence, the synaptic basis for the crossmodal effects following deafness occurs as increases in synaptic spine density and size on the dendrites of pyramidal neurons in the supragranular layers of the FAES (Clemo et al., 2014).

Sensory deprivation not only influences crossmodal plasticity in the AESc and the attendant within-modality processing, it also dramatically impacts multisensory processing as well. A recent dark-rearing (in contrast to binocular lid-suture) experiment by Carriere et al. (Carriere et al., 2007) revealed that the overall sensory representations of AES remained intact in these animals, including predominant visual responses in AEV, but the balance of multisensory interactions was shifted such that, 1) a greater proportion of AES neurons were modulated rather than driven by a second sensory modality, and 2) a greater proportion of neurons yielded response depressions resulting from spatially and temporally coincident stimuli. Thus normal sensory experience appears to guide the maturation of multisensory circuits to generate the appropriate balance of excitation and inhibition subserving multisensory interactions. More subtle alterations in sensory experience also influence multisensory processing. For instance, animals that were reared in an environment with a fixed spatial disparity (in which auditory and visual stimuli were presented simultaneously but 30° apart using prisms) exhibited multisensory response enhancements in AES that were preferentially attuned to a 30° disparity rather than to spatially coincident audiovisual stimuli (Polley et al., 2008; Wallace & Stein, 2007). Similarly, when temporal components were manipulated such that an auditory stimulus always lagged a visual stimulus by 100ms in rearing conditions, this temporal delay (rather than temporally coincident stimuli) produced maximal multisensory enhancements (Polley et al., 2008). When this delay was extended to 250ms, multisensory integration was abolished, indicating that multisensory interactions are malleable during the course of development, but that certain constraints for binding stimuli into a unified percept continue to exist. Ultimately, these collective studies on the AESc have provided an unrivaled view into the process of crossmodal plasticity and its ensuing effects on intra-modal as well as multisensory processing.

Potential functional roles of AESc

While awake and behaving neurophysiological recordings in AES cat have not been undertaken thus far, evidence from combined physiological and anatomical studies give great insight into AES function. Here, we will summarize studies focusing on potential functional roles of AES as a whole. Emphasis will be placed on discussing the contributions of multisensory processing to perception and behavior. As mentioned earlier, prior research has shown AES involvement in auditory and visual motion processing (Clarey & Irvine, 1986, 1990b; Kimura & Tamai, 1992; Kimura et al., 1996; Nakai et al., 1987; Tamai & Miyashita, 1989; Tamai et al., 1989) and sound localization (Lomber et al., 2007; Malhotra & Lomber, 2006; Malhotra et al., 2004) as well as gating multisensory integration at the subcortical level (Alvarado et al., 2007; Alvarado et al., 2008). Furthermore, research findings hint at a potential role in sensorimotor and sensory coordinate transformation.

AES gates multisensory integration in the midbrain

The interaction of AES with superior colliculus (SC) has been one of the most studied roles of AES thus far. As described earlier, all subregions of AES project to the intermediate and deep layers of SC. With that in mind, a host of studies originally hypothesized that these projections could be the major driving inputs of unisensory and maybe multisensory signals to SC. Indeed, AES has been shown to play a crucial role in mediating proper multisensory processing in the midbrain (Jiang & Stein, 2003; Stein et al., 2002; Wallace & Stein, 1994) as studies looking at AES ablation or reversible deactivation (Figure 2-3a, left panel) in neonates and adult cats revealed a significant lack of multisensory integration in the SC (Jiang et al., 2006; Wallace & Stein, 1994). Interestingly, while multisensory integration is almost entirely abolished without AES stimulation, SC neurons show normal unisensory response profiles as well as normal unisensory-unisensory integration (Figure 2-3a, right panel) even in the same neuron (Alvarado et al., 2007; Wallace & Stein, 1994). Research looking at developmental trajectories of AES and SC also revealed a tight link between appearance of sensory responsiveness of AES neurons and multisensory integration in SC. Moreover, deactivation of AES during development diminishes the integrative capacity of SC neurons at all tested time points (Figure 2-3b). How such AES control over SC integration is realized, remains unknown. One proposed model (Figure 2-3c) suggests that while non-association areas may be sufficient to build a multisensory SC neuron, only association cortex (i.e. AES) can ensure multisensory integration (i.e. the non-linear transformation of bimodal inputs). Further studies also explored the direct implications of AES deactivation on multisensory orientation behaviors and found strong deficits when crosstalk between AES and SC was disrupted.

The effect of deactivation on behavioral outcomes was assessed by administering lidocaine to temporarily deactivate the FAES/AEV region of AES during behavioral trials (Wilkinson et al., 1996). Deactivation had no effect on responses to unimodal cues (animals would still orient toward and approach an LED to obtain a food reward), but profoundly impacted the response to audiovisual cues such that the normal enhancement of responses (increased accuracy when an auditory cue was presented with a visual cue) was greatly reduced. Similarly, when the entirety of AES was lesioned together with rLS, animals lacked the behavioral benefits from audiovisual stimulus combinations when trying to localize targets in contralateral space (Jiang et al., 2007). Thus, AES appears to serve as a gating mechanism for multisensory processing in SC that renders it necessary for the synthesis of multiple sensory cues that ultimately produces behavioral benefits including enhanced detection and orientation.

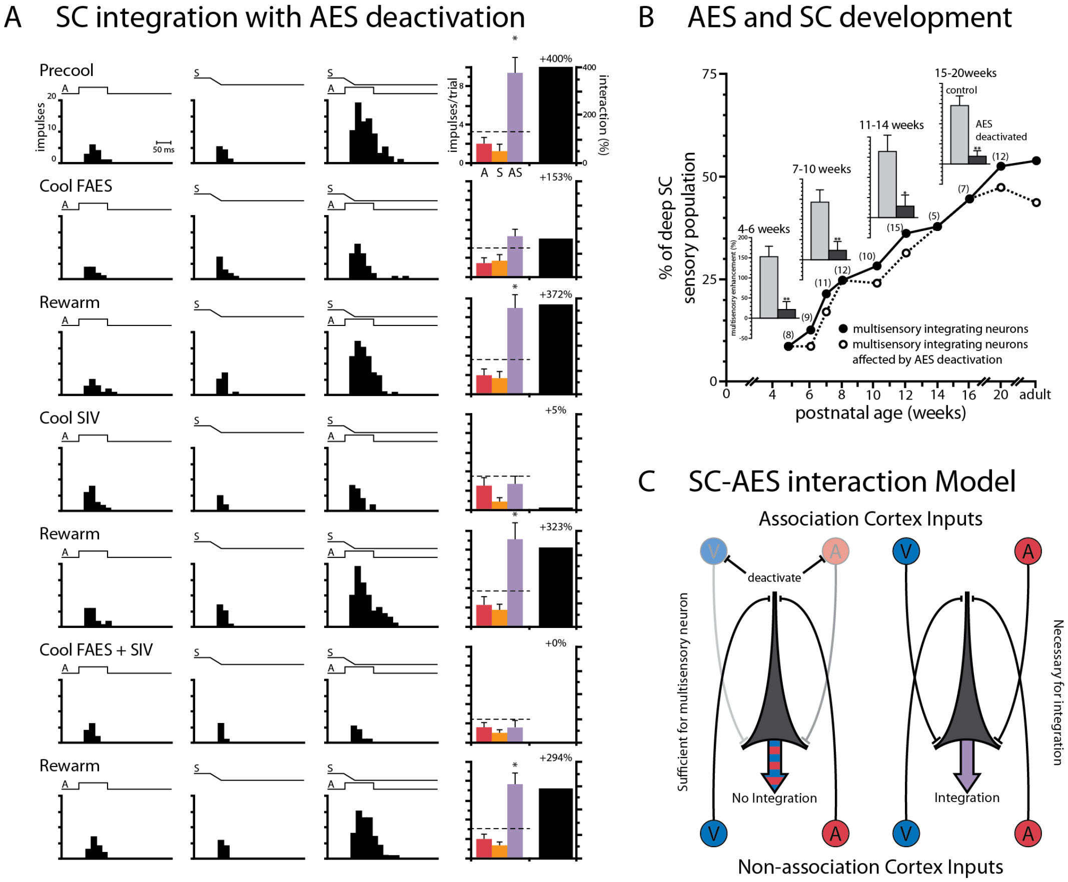


Figure 2-3: **A** – Effects on multisensory integration in superior colliculus (SC) after cooling of subdomains of anterior ectosylvian sulcus (AESc). **B** – Trajectories of the emergence of unisensory and multisensory neurons in AESc and SC. **C** – Model of SC-AES interactions. Color conventions are as follows; somatosensory – orange, visual – blue, and auditory – red, and multisensory – purple.

AES is part of a sensorimotor loop

As delineated earlier, AES projects to SC (Fuentes-Santamaria et al., 2008; Meredith & Clemo, 1989; Tamai & Miyashita, 1989; Wallace et al., 1993), which has a large population of neurons gating orientation behaviors (Burnett et al., 2004; Ciaramitaro et al., 1997; Munoz & Guitton, 1989; Peck, 1984; Peck, 1996; Pelisson et al., 1995; Roucoux et al., 1980). SC has been indicated to crosstalk with the frontal eye fields (FEFs) (Jiang et al., 2002; Wilkinson et al., 1996) as well as downstream with motor brainstem nuclei and the cerebellum (Guitton & Munoz, 1991; Meredith & Stein, 1985; Munoz & Guitton, 1991; Ogasawara et al., 1984; Olivier et al., 1993; Pare & Guitton, 1994). Given the influence of AES on multisensory integration in the SC and SC projection patterns to motor regions, AES appears to be part of sensorimotor loop that is highly influenced by multisensory processing. In fact, a few studies looking at cortical control of multisensory orientation behaviors have shown significant deficits with the ablation or reversible deactivation of AES (Jiang et al., 2007; Stein et al., 2002; Wilkinson et al., 1996). Furthermore, direct connections between AES and motor regions also exist (Reinoso-Suarez & Roda, 1985; Scannell et al., 1995). A distinct group of neurons in AEV for example project directly to the frontal eye fields (Nakai et al., 1987; Tamai et al., 1989), an interesting finding which needs to be explored further. Injecting the multisensory borders remains technically difficult as they are located buried within the sulcus and thus whether or how multisensory neurons contribute to this sensorimotor loop remains to be determined.

AES may be involved in sensory coordinate transformation

Multisensory structures in the primate brain have been implicated to play a crucial role in coordinate transformation between the senses. Schlack et al 2005 for example studied the ventral intraparietal area (VIP) in macaques with focus on receptive field (RFs) architecture of the constituent unisensory receptive fields, in particular matching head-centered and eye-centered RFs during multisensory conditions (Schlack et al., 2005). Given that AES is similarly tasked with ensuring the appropriate integration of multiple modalities, it appears intuitive that AES could be involved in sensory coordinate transformation. Indeed, Wallace and colleagues have shown that visual and auditory receptive fields in AES, albeit overlapping, show great heterogeneity, which may be beneficial when trying to match head-centered and eye centered coordinates (Carriere et al., 2008; Royal et al., 2009). Future studies need to determine whether AES actively can transform RFs in an awake and behaving setting.

AES in other species

While potential non-human and human primate homologues to AES are still unknown, with its substantial population of multisensory neurons, its location at the junction of parietal, frontal, and temporal cortex, AES reminds of superior temporal sulcus (STS) (Clemo et al., 2012), in particular posterior STS (pSTS). In fact, many similarities have been observed. Both structures receive major inputs from secondary unisensory association regions (Cappe & Barone, 2005; de la Mothe et al., 2006; Hackett et al., 1999; Seltzer & Pandya, 1978, 1994; Yeterian & Pandya, 1995), have zones with separated and overlapping inputs from multiple modalities (Lewis & Van Essen, 2000; Seltzer & Pandya, 1978; Seltzer et al., 1996), and actively integrate multiple sensory cues as investigated via spikes and local field potentials in primates (Benevento et al., 1977; Bruce et al., 1981; Chandrasekaran & Ghazanfar, 2009; Ghazanfar et al., 2010; Hikosaka et al., 1988; Maier et al., 2008) as well as functional imaging in humans (Calvert et al., 2000; Hocking & Price, 2008; Murase et al., 2008; Stevenson & James, 2009; Stevenson et al., 2007; Werner & Noppeney, 2010; Wright et al., 2003). However, substantial differences do exist. While AES is made up of distinct unisensory areas and multisensory border sections, STS mostly contains clusters of multisensory neurons interspersed within its sensory modality representations (Clemo et al., 2012). The best evidence of an AES-like architecture stems from an imaging study of human cortex by Beauchamp and colleagues revealing a patchy organization of unisensory zones with adjacent multisensory borders (Beauchamp et al., 2004). One other strong difference arises from differential inputs between AES and STS in that AES receives strong projections from somatosensory cortices while STS has only sparse connections with somatosensory regions (Seltzer & Pandya, 1994).

Are parts or all of AES an extension of insula?

One peculiar fact that remains to be solved is what makes AES one functional unit. For example, visual AEV appears misplaced and far away from other extrastriate visual regions while auditory field AES and area SIV are immediately adjacent to auditory and somatosensory cortices, respectively. The fact that these three regions have multisensory borders is one of the reasons research has focused on AES as one functional structure. But does spatial proximity make a functional unit? Indeed, Scannell and colleagues demonstrated that areal proximity is the strongest predictor for corticocortical connectivity (Scannell et al., 1995). But does AEV connect with FAES and SIV or with insula the most? As mentioned earlier, while FAES and SIV appear to strongly interconnect and influence each other’s unimodal processing (Dehner et al., 2004; Meredith et al., 2006), non-dominant sensory interactions in AEV have not been demonstrated.

Moreover, interestingly, a distinct border between ventral AEV and dorsal insula cannot be determined. Various anatomical studies investigating both AES (Mucke et al., 1982; Norita et al., 1986) and insula (Clasca et al., 1997, 2000) utilizing a variety of neuroanatomical stains have failed to convincingly characterize an AEV/insula border.

Furthermore, the anterior sylvian area (AS) of insula (the region immediately ventral to AEV) has sensory processing features similar to AES and AEV in particular (Benedek & Hicks, 1988; Benedek et al., 1986; Fallon & Benevento, 1977; Hicks et al., 1988a, 1988b) as well as similar connection patterns (Hicks et al., 1986; Olson & Musil, 1992; Rodrigo-Angulo & Reinoso-Suarez, 1995; Shimizu & Norita, 1991); so much so that some studies do not even distinguish between the two regions (Benedek et al., 1996; Hicks et al., 1988b). Thus, the following question arises: Could it be that AEV belongs to insula while SIV and FAES are just bordering association regions?

Indeed, this notion may be justified based on already published anatomical and physiological data. For example, when looking at Figure 2-4, it becomes clear that not just AES' proximity to somatosensory and auditory cortex may suggest that but also the level of processing hierarchy (based on anatomical inputs) markedly differs between FAES/SIV and AEV. Input patterns of AEV robustly resemble those of AS (one sensory subregion of insula, Figure 2-5) compared to the other two subdivisions. AEV receives strongest projections from other higher-order cortical regions (past secondary cortices) while SIV and FAES have direct inputs from primary and secondary somatosensory and auditory cortices, respectively. Furthermore, as discussed earlier, AEV and insula preferred rapidly moving visual stimuli and often showed directional specificity (Benedek et al., 1988; Mucke et al., 1982; Olson & Graybiel, 1983, 1987; Scannell et al., 1996), with the exceptions that insular cortex preferred somewhat lower stimulus velocities and larger stimuli overall (Benedek et al., 1986; Benedek et al., 1996). Considering AEV part of the insula does not diminish findings characterizing the multisensory border regions of AES. In fact, these border regions may provide a much more specific purpose, which will be discussed next. AES' unique location adjacent to sensory cortices, insular cortex, and prefrontal regions could allow it to integrate sensory information along multiple sensory pathways as well as information of stimulus properties such as object characteristics and locations. Here, the AES border regions could play a very crucial role by integrating multisensory cues with information about spatial and temporal stimulus features. Thus, an additional question about the utility of AES arises when thinking about the what (ventral) versus where (dorsal) pathways and the possibility that the subdivisions of AES belong to those two different streams and that the multisensory border regions may be a hub for integrating these parallel pathways across multiple senses.

Processing Levels of AES Inputs

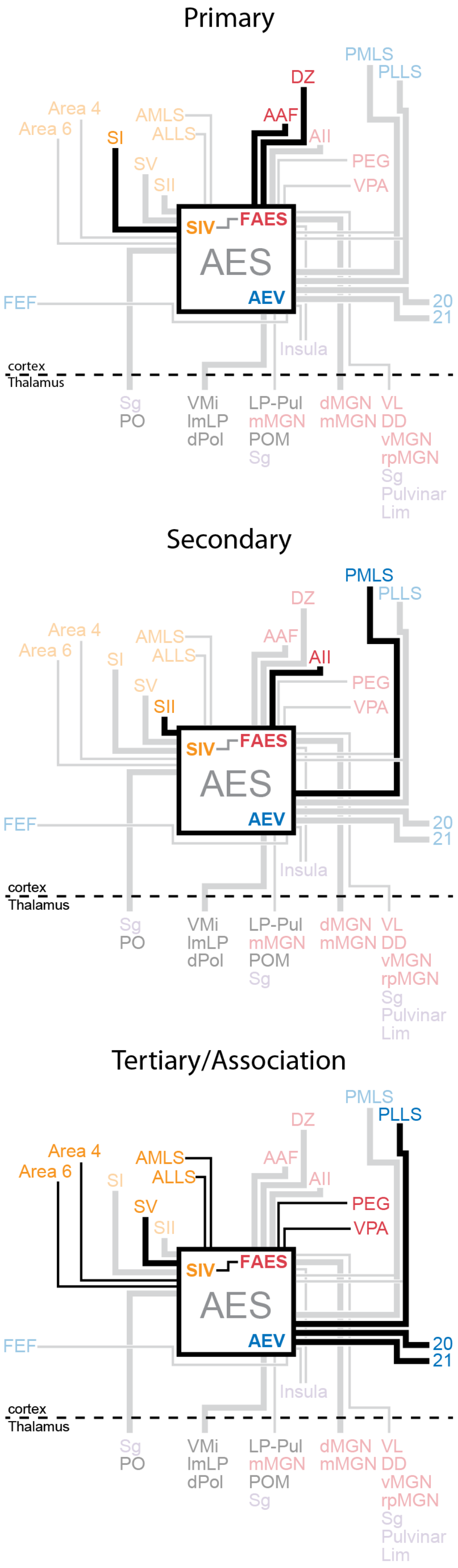


Figure 2-4: Circuit diagrams of inputs to the three domains of anterior ectosylvian sulcus (AESc) separated by ‘processing’ level. Color conventions are as follows; somatosensory – orange, visual – blue, auditory – red, multisensory – purple, and other - black. Abbreviations: see abbreviation list.

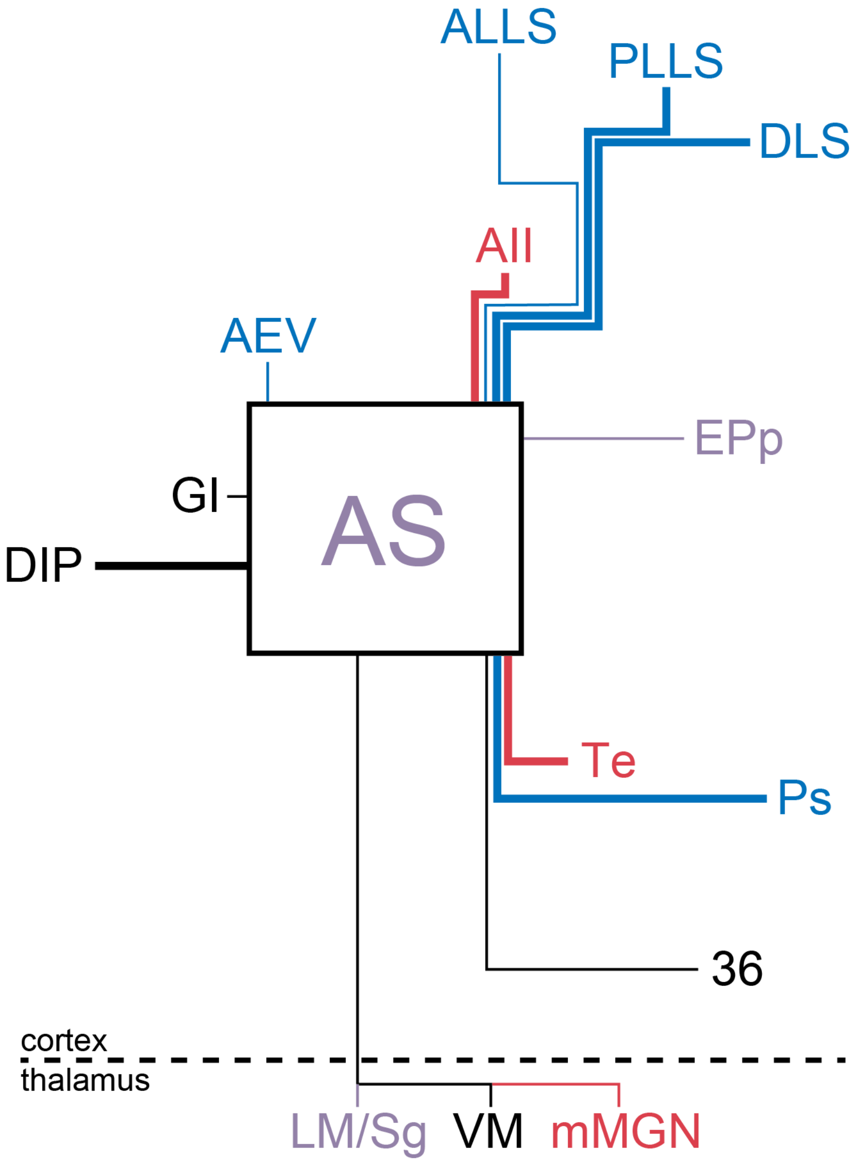


Figure 2-5: Circuit diagrams of inputs to the anterior sylvian area of insula. Color conventions are as follows; visual – blue, auditory – red, multisensory – purple, and other - black. Abbreviations: see abbreviation list.

What versus where pathways

While the dorsal and ventral stream segregation has been primarily studied in the visual system (space and object), studies of the auditory pathway have suggested similar dual streams identifying auditory objects through spectrotemporal sound properties (ventral) and auditory space through sound localization processing (dorsal) (Cloutman, 2013; Lomber & Malhotra, 2008; Rauschecker, 1997). Additionally, dorsal streams are often specifically tasked with providing sensory guidance for motor action through sensorimotor integration (Cloutman, 2013). As mentioned earlier, AES is a prime candidate region to integrate these parallel streams across the senses.

When examining prior studies in detail, physiological and anatomical evidence suggests that AEV, FAES, and SIV subserve those pathways differentially. FAES and SIV both illustrated strong spatial selectivity. For instance, SIV is characterized by a somatotopic map with areas of best responsivity, which offers a great substrate for localizing somatosensory cues. Moreover, FAES has been directly linked to sound localization via cooling studies with animals showing strong localization deficits during FAES inactivation (Lomber et al., 2007). Additionally, one study finds evidence for an auditory spatial map in FAES (Rauschecker, 1997). One of the hallmarks of the dorsal pathway lies within response latencies. Given that timing is very important to a system that cares about motion and location, latencies in the dorsal pathway are often shorter than in the ventral pathway, even if areas from both streams have similar stimulus preferences [cite here]. Both, FAES, and SIV, show markedly shorter latencies than AEV, besides being tested with preferred stimuli. While AEV does show direction specificity and a preference for moving stimuli, this appears to be heavily tied to pattern processing (Nagy et al., 2003). Indeed, AEV strongly prefers drifted gradients as well as plaid patterns over simple stimuli or other patterns, hinting at a prospective involvement in ventral stream processing. Furthermore, its possible association with insular cortex strengthens its potential role in signaling object features considering that a host of studies in humans and non-human primates link insular activation to object recognition paradigms (Nieuwenhuys, 2012).

CHAPTER III

AUDIOVISUAL INTERACTIONS IN CAT INSULA ARE MODULATED BY SPATIAL AND TEMPORAL FACTORS

This chapter is a manuscript in preparation for submission to the 'Journal of Neurophysiology' as: Krueger Fister J, Nidiffer AR, Kurela LR, and Wallace MT. Audiovisual interactions in cat insula are modulated by spatial and temporal factors

Introduction

In order to successfully navigate our daily environment, the brain is tasked with properly processing sensory information from multiple modalities simultaneously. To do so, sensory cues from the same source are integrated, resulting in numerous behavioral and perceptual benefits. These include but are not limited to speeded response times (Amlot et al., 2003; Bernstein et al., 1969; Hecht et al., 2008), increased accuracies (Frassinetti et al., 2002), improved detection rates (Lovelace et al., 2003), enhancements in speech and language comprehension (Erickson et al., 2014; Giraud et al., 2001; Liu et al., 2013; MacSweeney et al., 2002), and improvements of various cognitive processes such as crossmodal attention, task switching, and working-memory (for more comprehensive reviews see Calvert et al. (2004); *The neural bases of multisensory processes* 2012); Shi and Muller (2013)).

Specialized regions such as the superior temporal sulcus or regions within parietal cortex have been implicated with actively integrating multisensory signals subserving the aforementioned behavioral and perceptual gains (for a review of multisensory regions see (Stein & Stanford, 2008)). Recent fMRI evidence in humans and anatomical and physiological work in primates extends this to insular cortex, which has substantial connections with sensory and cognitive networks (Nieuwenhuys, 2012) and strong multisensory convergence (Cavada et al., 2000; Frank et al., 2014; Hashimoto et al., 2013). Research in humans investigating characteristics of multisensory processing has shown that activity in insula is enhanced during multisensory conditions (Gentile et al., 2011) and that insula is preferentially active for temporally or spatially congruent over incongruent stimuli (Naghavi et al., 2007; Teder-Salejarvi et al., 2005; Zeller et al., 2015). Additionally, illusory percepts such as the ventriloquism effect or the rubber hand illusion have also been linked to insula activation. (Bischoff et al., 2007; Zeller et al., 2015)

With insula's manifold connections to various regions of the brain, one of its most notable functions is its role in integrating intero- and exteroceptive cues (Chang et al., 2013; Jones et al., 2010; Kurth et al., 2010; Menon & Uddin, 2010; Mutschler et al., 2009; Nieuwenhuys, 2012; Ohira, 2014). Supporting this role is its well-established anterior-posterior axis where anterior portions deal with signals from limbic and cognitive networks and posterior portions process signals from sensory and motor fields (Nieuwenhuys, 2012) . Combining different networks in a manner like insula makes it an excellent candidate region to integrate information from different senses across these loops and by extension a great structure to investigate multisensory integration in the context of perception and behavior. Nevertheless, while previously mentioned studies clearly suggest that insula has a role in multisensory processing, underlying mechanistic features remain to be elucidated. In addition to this, how multisensory interactions contribute to any functional roles of insula has yet to be determined.

A tremendous amount of progress, however, has been made in characterizing multisensory neurons in other regions, and studies across multiple species have identified a set of principles of multisensory integration. Unisensory stimuli that are weakly effective but temporally and spatially coincident when paired together are more likely to be integrated and produce response enhancements (Meredith & Stein, 1983, 1986a; Meredith et al., 1987). These principles indeed hold true at the neural level across subcortical (i.e. cat and primate: superior colliculus (Wallace & Stein, 1996; Wallace et al., 1996)) and cortical (i.e. cat: anterior ectosylvian sulcus (Wallace et al., 1992), posterosuprasylvian areas (Allman & Meredith, 2007; Clemo et al., 2007); primate: superior temporal sulcus (Barraclough et al., 2005)) brain regions in various species (rodents (Ramachandran et al., 1993), cats (Perrault et al., 2012), primates (Wallace et al., 1996), humans (Bolognini et al., 2010; Stevenson & James, 2009)); for reviews on methods see (Calvert & Thesen, 2004; Stanislaw, 1988; Stein et al., 2009; Stevenson, Ghose, et al., 2014)), and at the behavioral level (for example in cats (Stein et al., 1988) and humans (Hairston, Laurienti, et al., 2003; Stevenson & James, 2009; Wallace et al., 2004)). Recent studies in our lab have further detailed a strong interrelationship between these factors at the single neuron level in animal studies (Carriere et al., 2008; Ghose & Wallace, 2014; Krueger et al., 2009; Royal et al., 2009), as well as in human performance (Krueger Fister et al., 2015 (in rivision); Nidiffer et al., 2015 (in revision); Stevenson, Fister, et al., 2012). Yet, how this affects multisensory processing on an intermediate level in the context of network activity remains to be elucidated.

Recently, studies have begun to highlight microcircuit interactions (i.e., along one cortical column) during multisensory stimulation utilizing multilaminar electrodes measuring local field potentials (LFPs). Indeed, in auditory cortex for example investigating microcircuits in such a manner, revealed differential feed-forward and feedback mechanisms of modulatory interactions (Ghazanfar & Schroeder, 2006; Schroeder & Foxe, 2002; Schroeder & Foxe, 2005; Schroeder et al., 2003). While these modulatory interactions are undoubtedly important (and have recently received a lot of attention as potential novel mechanisms underlying perception and behavior (Foxe et al., 2002; Molholm et al., 2002; Murray et al., 2006)), investigations into microcircuit interactions in more traditional multisensory areas in association cortex such as insular cortex have not been undertaken.

Thus the current study sought to investigate multisensory interactions across the cortical mantle in cat insula in order to begin characterizing multisensory processing mechanisms within neural association networks. A large number of prior studies providing a neurophysiological and anatomical framework for multisensory integration in subcortex and cortex make the cat a pertinent animal species to investigate such multisensory circuits. Furthermore, insula's location at the parito-temporal-frontal junction in cat cortex (Clasca et al., 1997) and its extensive, reciprocal connections with sensory, motor, and limbic fields (Benedek et al., 1996; Clasca et al., 2000; Hicks et al., 1988a) suggest it to be a multisensory hub . Indeed, posterior portions are thought to be part of sensory(motor) loops and anterior portions of limbic networks (Clasca et al., 1997, 2000) similarly to what has been observed in primates (Cavada et al., 2000; Mesulam & Mufson, 1985) and humans (Mesulam & Mufson, 1985; Nieuwenhuys, 2012)

Because of its extensive inputs from multiple sensory modalities as well as noted conservation across species, the insula is a prime candidate to evaluate the contributions of multisensory processing to perception and behavior. Characterizing insular microcircuit activity is a first step to assess such network properties. Thus, the current study utilized simultaneous laminar recordings of local field potentials (LFPs) to evaluate multisensory microcircuits within one posterior insular region, the anterior sylvian area, which has been previously shown to contain bimodal and trimodal neurons (Hicks et al., 1988a). Specifically, three key questions were pursued in the current study. First, whether multisensory interactions are observable in LFPs in the cat insula. Second, if these multisensory interactions are affected by stimulus features such as space, time, relative effectiveness, and the interrelationships between these stimulus factors, Finally, we examined whether there are laminar differences during multisensory integration.

Methods

General procedures

3 adult cats underwent terminal extracellular recordings in insular and surrounding cortex utilizing a 16 or 24 channel laminar U-probe (Plexon Inc). Data were collected during auditory, visual, and auditory-visual stimulation. At the end of the recording portion of the experiment, animals were euthanized and perfused. All experiments took place under anesthesia and were performed in compliance with the *Guide for the Care and Use of Laboratory Animals* at Vanderbilt University Medical Center, which holds and accreditation by the American Association for Accreditation of Laboratory Animal Care.

Surgical and recording procedures

At the beginning of each terminal experiment, cats were induced with ketamine hydrochloride (20 mg/kg, IM) and acepromazine maleate (0.04 mg/kg, IM). Subsequently, animals were intubated and artificially respirated. Anesthesia was maintained via inhalant isoflurane (<2%) for the duration of the surgical procedure. Vital signs, including heart rate, blood pressure, core temperature, expiratory CO2, and SPO2 levels were monitored and recorded using a specialized vital sign monitor (VetSpecs monitor, VSM8 or a Scil monitor). A craniotomy was made over insular and adjacent cortex. A stainless steel head holder was affixed to the skull using surgical screws and dental cement at the top of the skull over the midline. This design ensured a recumbent positioning of the animal without obstructing the visual or auditory fields. Once the surgery was completed, the animal was switched from the surgical stereotaxic apparatus to a customized head restraint matching the implanted head holder and situated to avoid prolonged pressure points in a natural sitting position. Once this was completed, the animal was put on a continuous infusion of ketamine (5 mg/kg/hr, IV) through the saphenous vein to maintain a stable plane of anesthesia during the recording portion of the experiment. Vecuronium bromide (0.2mg/kg/hr, IV) or rocuronium bromide ([conc]), both neuromuscular blocking agents, were added to the continuous infusion in order to ensure paralysis necessary to prevent ocular drift. Subcutaneous fluids were provided throughout the entire experiment. Single microelectrodes (parylene-insulated, tungsten, Z = 1.5-4 mΩ at 1 kHz) were advanced into target regions (insula and surrounding cortex) and multi-unit activity was characterized to map the region's electrophysiological properties, such as general responsiveness and stimulus preferences (auditory, visual, and auditory-visual). Neural activity was amplified, recorded, and stored through a Plexon 16 - 32 channel MAP system. When mapping was completed, a 16 or 24 channel laminar U-probe (channel spacing: 125 μm, distance from electrode tip to first channel: 700μm, Z = ~1mΩ) was placed into the target regions. Care was taken to choose a recording depth that ensures channel distribution across all cortical layers, which conservatively led to 2 – 3 different recording depths per recording location if necessary when using the 16 channel electrode.

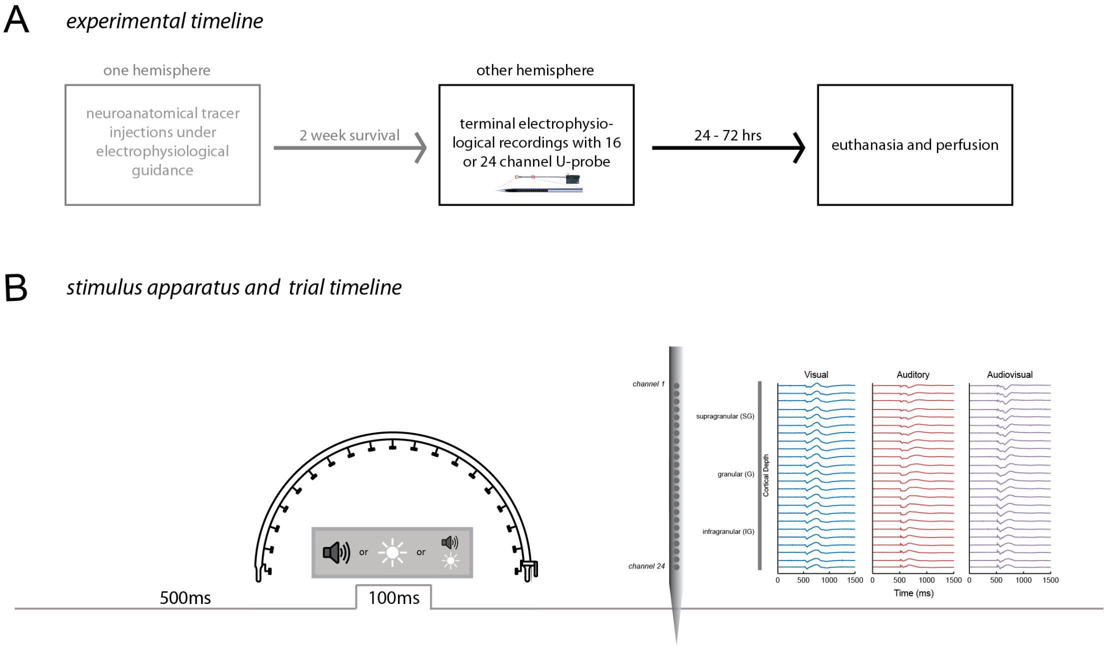


Figure 3-1: **A** – Experimental timeline. **B** – Recording trial structure with 500ms pre-stimulus interval, 100ms stimulus presentation, and then at least 1000ms post-stimulus interval. Stimuli included auditory only (A-red), visual only (V-blue), and audiovisual (AV-purple) at various locations (several azimuths and several elevations).

Stimulus presentation and trial conditions

Light-emitting diodes (LEDs) and speakers were mounted together every 10° (azimuth) on a hoop, which could be rotated along its axis at 10° (elevation) increments (Figure 3-1b). Due to the constraints of the table on which the cat was situated, stimuli could be presented from -40° to 90° elevation and -90° to 90° azimuth (see Figure 3-1). Visual stimuli were 100 ms single LED flashes (luminance 104 cd/m^2), presented to the contralateral eye to the recording electrode. The ipsilateral eye was occluded throughout recordings. Auditory stimuli consisted of 100 ms broadband noise bursts (20 Hz – 20 kHz, 67 dB SPL, background: 45 dB SPL). Stimulus conditions included unisensory visual and auditory trials as well as spatially coincident multisensory audiovisual trials with various stimulus onset asynchronies (auditory preceding visual by 50 ms (V50A0), objectively simultaneous (V0A0), and visual preceding auditory by 50ms, 100ms, 150ms, and 200ms (V0A50, V0A100, V0A150, V0A200)). Unisensory and multisensory stimuli were played in pseudorandom order across multiple azimuth and elevations within the receptive field of the sampled insular region.

Experimental procedure

The present study was part of a larger investigation. Briefly, on day one of the experiment, the cat underwent surgery, which included a craniotomy over the target area, anterior sylvian area (AS), as well as surrounding regions such one hemisphere. Anterograde and retrograde tracer cocktails were injected under electrophysiological guidance (Figure 3-1a, panel 1). After about a two week survival period, a 24-72 hr terminal recording experiment was commenced on the other hemisphere (Figure 3-1a, panel 2). The present study focuses on the data obtained during this portion of the experiment. The target region was initially mapped with a single electrode to delineate border regions in order to guarantee equal sampling of recording locations. Once a recording location was chosen, the U-probe was slowly advanced into the brain tissue. Several pauses were taken in order to let the tissue settle in place. All channels were continuously monitored for activity changes via Plexon Inc software, oscilloscope, and audio analyzer until placement depth was satisfactory and spanning all cortical layers. Often multiple recording depths were sampled in order to guarantee all layers are represented. With the U-probe in place, receptive fields were roughly mapped and 2-3 azimuthal locations over 3-5 elevations were chosen. Auditory, visual, and audiovisual stimuli were pseudorandomly sampled while neuronal activity was continuously recorded via the Plexon MAP server and associated software. In each animal, 8-10 different recording locations spanning AS with 2-3 recording depth were tested this way.

Data Analysis

Custom MATLAB scripts were used for all analysis. Recording files were imported into MATLAB and sorted by condition and channel. Mean voltages in multisensory conditions were compared to the voltages in constituent unisensory conditions in multiple ways: peak amplitudes, response magnitudes (area under the curve (AUC) values for the first 500ms after stimulus onset), and response latencies (sustained responses for 15ms over threshold with threshold being 2 standard deviations above baseline – 350ms before stimulus onset). Multisensory integration in peak amplitude and response magnitudes was assessed either by comparing it to the mean of the maximum unisensory response or by comparing it to a linear prediction

$$\widehat{AV} = A + V$$

where A and V are the mean evoked auditory and visual LFPs, respectively. Model predictions for response onsets were calculated by taking the minimum of the auditory and visual onsets while compensating for the respective lag of each stimulus at each particular SOA such that:

$$\widehat{Ons}_{AV} = min([Ons_A + Lag_A], [Ons_V + Lag_V])$$

Where $\widehat{Ons}_{AV}$ is the predicted onset at each SOA, Ons_A is the average onset during auditory only stimulation, Ons_V is the average onset during visual only stimulation, Lag_A is the delay applied to the auditory stimulus during audiovisual stimulation (zero during auditory-first and simultaneous presentation), and Ons_V is the delay applied to the visual stimulus during audiovisual stimulation (zero during visual-first and simultaneous presentation).

Statistical measures included repeated measures ANOVAs and paired sample t-tests.

Results

Local field potentials where measured in the anterior sylvian area (AS), which makes up part of the posterior portion of insula, Responses were obtained to auditory and visual stimuli as well as their combination whereby stimulus onset asynchrony (SOA) and stimulus location were parametrically varied. Generally, 9 or more locations were tested with 5 SOAs each.

Local field potentials show multisensory interactions

Both, auditory (A) and visual (V) stimuli evoked LFP changes across multiple cortical layers (Figure 3-2a left panel). Collapsing across the entire data set, auditory LFP responses were significantly greater than visual LFPs ($p_{(\text{response magnitude})} = 9.36 \times 10^{-7}$, $p_{(\text{peak amplitude})} = 1.18 \times 10^{-187}$, Figure 3-2b). Subsequently to this, a repeated measures ANOVA revealed significant main effects for modality. Specifically, audiovisual (AV) interactions were visible in overall magnitude (response magnitude is the area under the curve for the first 500ms after stimulus onset) and peak amplitude and significantly exceeded maximum unisensory responses (auditory, $p_{(\text{response magnitude})} = 3.5 \times 10^{-5}$, $p_{(\text{peak amplitude})} = 5.61 \times 10^{-67}$). Interestingly, they were also significantly subadditive compared to the linear prediction (A+V, $p_{(\text{response magnitude})} = 8.98 \times 10^{-40}$, $p_{(\text{peak amplitude})} = 0$, Figure 3-2b). Furthermore, striking latency reductions were observed during audiovisual stimulation with AV responses being significantly shorter than the fastest unisensory onsets (auditory, $p_{(\text{response onset})} = 1.93 \times 10^{-32}$, Figure 3-5a). With these findings indicating the presence of multisensory integration in insular cortex, a set of analysis followed exploring potential spatial and temporal influences on these processes.

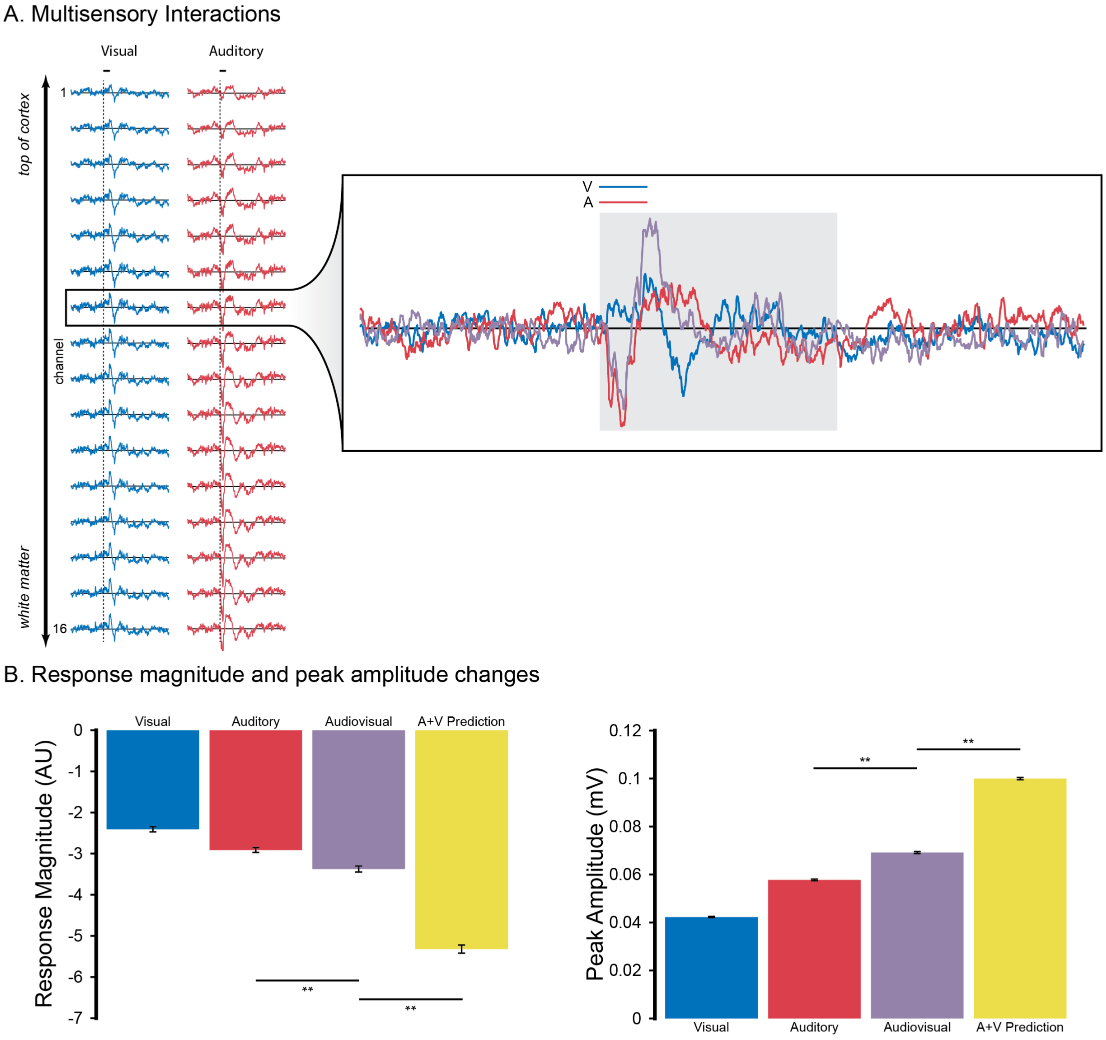


Figure 3-2: Audiovisual interactions show significant changes in response magnitude and peak amplitude. **A** - Exemplar local field potential traces from one recording. Visual (V - blue) and auditory (A - red). V and A LFPs were evoked across all layers. Inset shows data from one recording channel of all three conditions (V, A, AV - purple). Note here the different LFP response patterns. **B** – Population data. AV means response magnitudes (left panel) and mean peak amplitudes (right panel) differ significantly from the maximum unisensory response (here A) and from the linear prediction (A+V, yellow). ** $p<0.01$. Error bars are S.E.M.

Spatial and temporal influences on multisensory local field potentials

In addition to significant main effects of modality (which includes the tested SOAs) and recording channel, the repeated measures ANOVA also revealed significant main effects for elevation but not azimuth. This suggests that stimulus onset asynchrony and stimulus location (in particular elevation) may modulate the signal differentially. Thus in order to better characterize multisensory integration, further analysis focused on temporal and spatial factors and their impact on the observed audiovisual interactions.

Although, all SOAs had significant subadditive interactions at the level of response magnitude and peak amplitude ($p_{(\text{response magnitude})} < 0.01$ and $p_{(\text{peak amplitude})} < 0.01$ for all, Figure 3-3), AV and V50A0 (A preceding V by 50 ms) showed significantly increased peak amplitudes while only AV also showed significantly increased response magnitude compared to auditory alone stimulation (peak amplitudes: $p_{(V50A0)}$ = 1.85 x 10^{-32}, p(AV) = 5.61 x $10^{-67}$and response magnitude: p(AV) = 3.5 x 10^{-5}, Figure 3-3). All other SOAs either showed no interaction or significantly decreased peaks and magnitudes compared to maximum unisensory response (response magnitudes: $p_{(V50A0)}$ = 0.0987, $p_{(V0A50)}$ = 0.4712, $p_{(V0A100)}$ = 0.3208, $p_{(V0A150)}$ = 0.0257, p(V0A200) = 0.0431 and peak amplitudes: $p_{(V0A50)}$ = 0.3642, $p_{(V0A100)}$ = 9.91 x 10^{-5}, $p_{(V0A150)}$ = 7.55 x 10^{-4}, $p_{(V0A200)}$ = 1.18 x 10^{-187}, Figure 3-3).

Because simultaneous AV conditions (SOA 0ms) showed the most consistent significant interactions, subsequent spatial analysis was undertaken at that SOA. Again, all interactions were significantly subadditive (response magnitudes: $p_{(\text{above})}$ = 2.65 x 10^{-4}, $p_{(\text{below})}$ = 7.6 x 10^{-18}, $p_{(\text{horizontal})}$ = 4.35 x 10^{-14} and peak amplitudes: $p_{(\text{above})}$ = 9.75 x 10^{-167}, $p_{(\text{below})}$ = 5.59 x 10^{-54}, $p_{(\text{horizontal})}$ = 2.37 x 10^{-50}) but audiovisual peak amplitudes were always larger than maximum unisensory ones ($p_{(\text{above})}$ = 0.0013, $p_{(\text{below})}$ = 1.78 x 10^{-63},

$p_{(horizontal)} = 9.34 \times 10^{-22}$, Figure 3-4). Furthermore, response magnitude showed some spatial specificity in that only locations above or below the horizontal plane demonstrated significant increases in magnitude for AV compared to A ($p_{(above)} = 7.2 \times 10^{-5}$, $p_{(below)} = 0.016$, $p_{(horizontal)} = 0.3718$, Figure 3-4). Multisensory interactions at the spiking level often include changes in spike count as well as changes in response latencies (Ghose et al., 2012; Rowland & Stein, 2008; Royal et al., 2009). Thus, further analysis was undertaken to delineate potential response onset benefits under multisensory conditions.

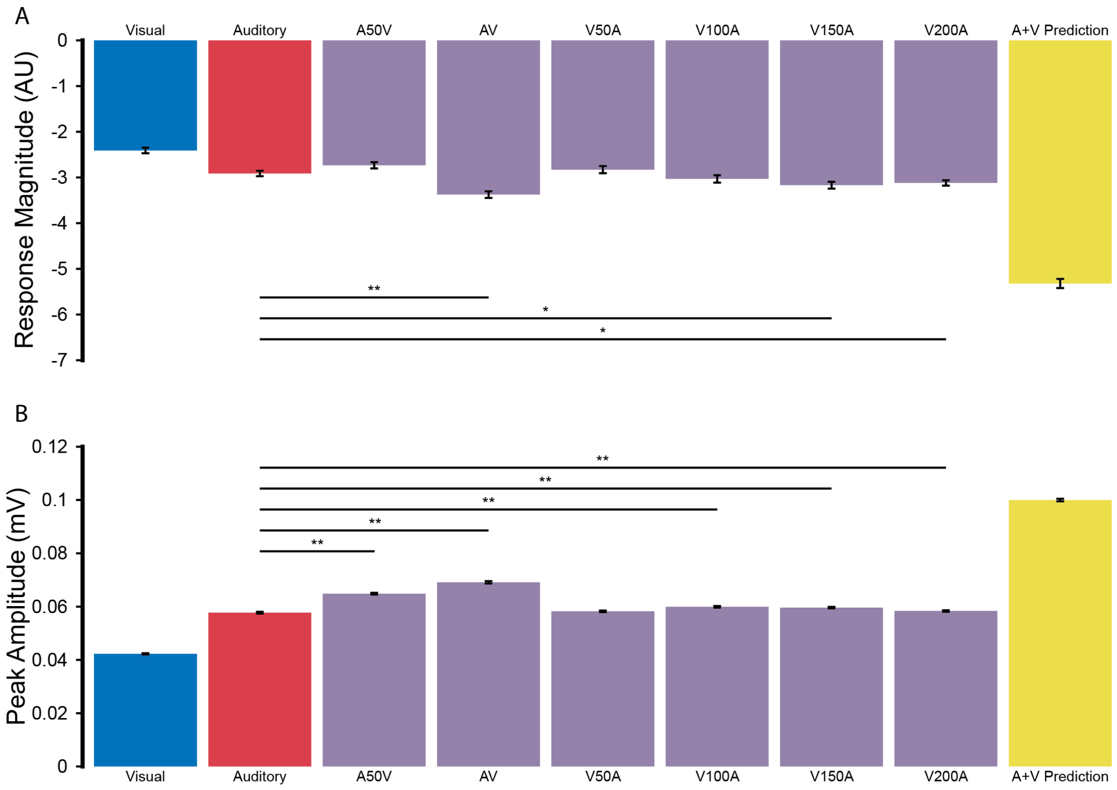
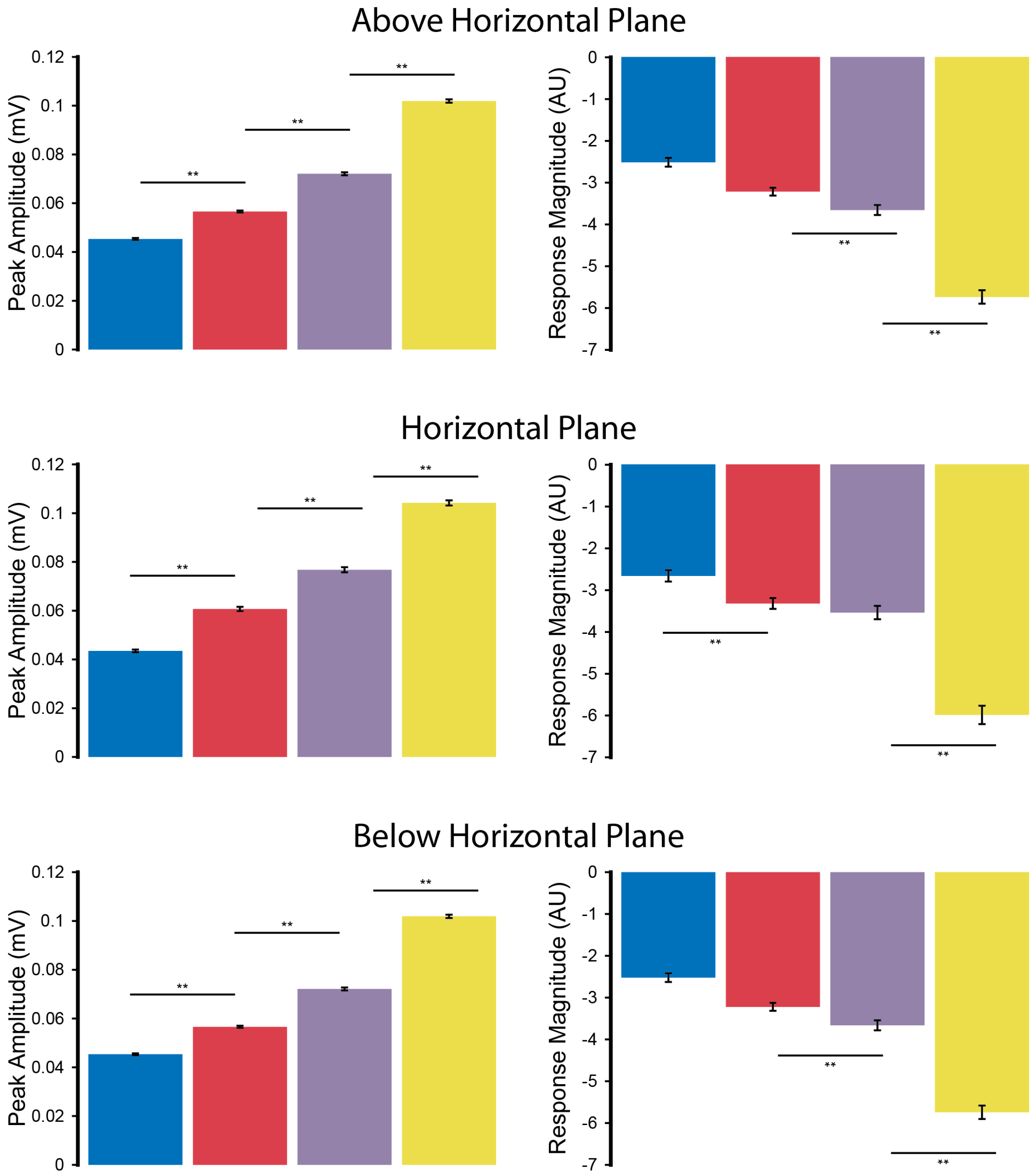


Figure 3-3: Stimulus onset asynchrony (SOA) significantly influences multisensory integration. **A** – Population data for V (blue), A (red), AV (purple), A+V (yellow) mean LFP magnitudes. AV mean magnitudes are significantly larger than auditory mean magnitudes for shorter SOAs and significantly smaller for longer SOAs and compared to the linear prediction. **B** - Population data for V (blue), A (red), AV (purple), A+V (yellow) mean LFP peaks. Again, AV peaks significantly exceed A peaks for short SOAs and are significantly smaller for long SOAs and compared to the prediction. Color convention the same as in A. **$p<0.01$ and *$p<0.05$. Error bars are S.E.M.



Above Horizontal Plane

Horizontal Plane

Below Horizontal Plane

Figure 3-4: Audiovisual interactions show some spatial specificity. AV peaks are significantly differed from A peaks (left panels) for all tested locations but AV response magnitudes are only significantly differed from A magnitudes for locations above and below the horizontal plane. Both measures were significantly subadditive for all locations. Color conventions are V (blue), A (red), AV (purple), A+V (yellow). $^{**}p<0.01$. Error bars are S.E.M.

Prominent response latency decreases mark audiovisual interactions

Not surprisingly, auditory LFP response onset is significantly earlier than visual LFP response onset ($p_{(response\ onset)} = 1.93 \times 10^{-32}$, Figure 3-5a and 3-5b). Audiovisual interactions however result in a significant speeding up of LFP latencies ($p_{(A50V0)} = 0.0015$, $p_{(AV)} = 1.93 \times 10^{-32}$, $p_{(V50A0)} = 3.56 \times 10^{-6}$, $p_{(V100A0)} = 1.34 \times 10^{-6,}$ $p_{(V150A0)} = 8.7 \times 10^{-60}$, $p_{(V200A0)} = 4.54 \times 10^{-92}$), which depended on SOA (Figure 3-5b). Here, largest latency benefits are observed when the auditory stimulus precedes the visual one or when they are objectively simultaneous. Yet, even long SOAs still result in significant changes in response onset indicative of multisensory integration in a way that is not predictable based on SOA (i.e. the latencies are not simply shifted by SOA). Evaluation of onset gain against a model prediction (Figure 3-5c) revealed that AV latencies were significantly different than predicted AV latencies ($p_{(A50V0)} = 0.0015$, $p_{(AV)} = 1.93 \times 10^{-32}$, $p_{(V50A0)} = 4.51 \times 10^{-48}$, $p_{(V100A0)} = 2.13 \times 10^{-13,}$ $p_{(V150A0)} = 1.62 \times 10^{-13}$, $p_{(V200A0)} = 0.0024$).

Latency decreases are restricted to the upper layers

For a subset of recordings (n = 13), which had the best electrode placements, a latency-by-layer analysis was undertaken. Across all layers, as expected visual signal latencies were always significantly slower than auditory or audiovisual ones ($p_{(response\ onset)} < 0.01$ for all). Significant differences between layers for visual onsets were found for locations above and in the horizontal plane, while significant differences between layers for auditory and audiovisual onsets were found for locations below and in the horizontal plane (visual: $p < 0.01$ for all, auditory: $p < 0.05$ for all and audiovisual: $p < 0.05$ for all). Significant interaction effects were restricted to layers I-IV and were observed for all tested locations (SG: .$p_{(above)} = 0.008$, $p_{(below)} = 0.003$, $p_{(horizontal)} = 0.001$, G: $p_{(above)} =$

0.038, $p_{(below)}$ = 0.005, $p_{(horizontal)}$ = 0.029 and IG: $p_{(above)}$ = 0.07, $p_{(below)}$ = 0.06, $p_{(horizontal)}$ = 0.24) Here, audiovisual onsets were always significantly shorter than auditory or visual latencies (Figure 3-6). Interestingly, the smallest latencies of the auditory signal were located in infragranular layers irrespective of stimulus location suggestion a potential ceiling effect resulting in no significant changes in latencies under multisensory conditions for those layers.

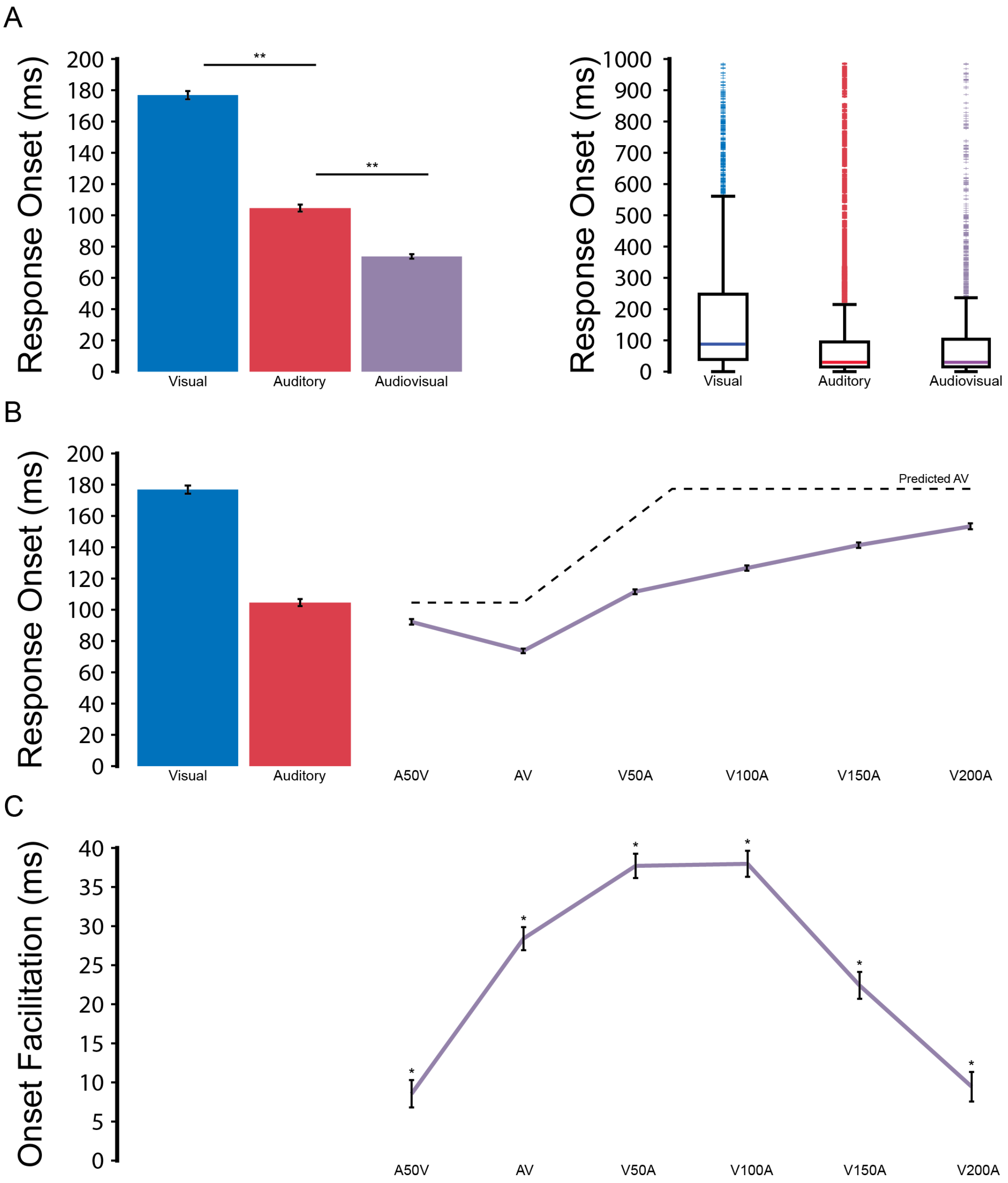


Figure 3-5: Response latency shifts show significant interactions across several SOAs. **A** – Generally, AV response latencies were significantly faster than the auditory onsets. **B** – Shorter SOAs show significant decreases in response onsets while longer SOAs do not. **C** – Onset facilitations for all tested SOAs. Color conventions are V (blue), A (red), AV (purple), A+V (yellow). **p<0.01 and *p<0.05. Error bars are S.E.M.

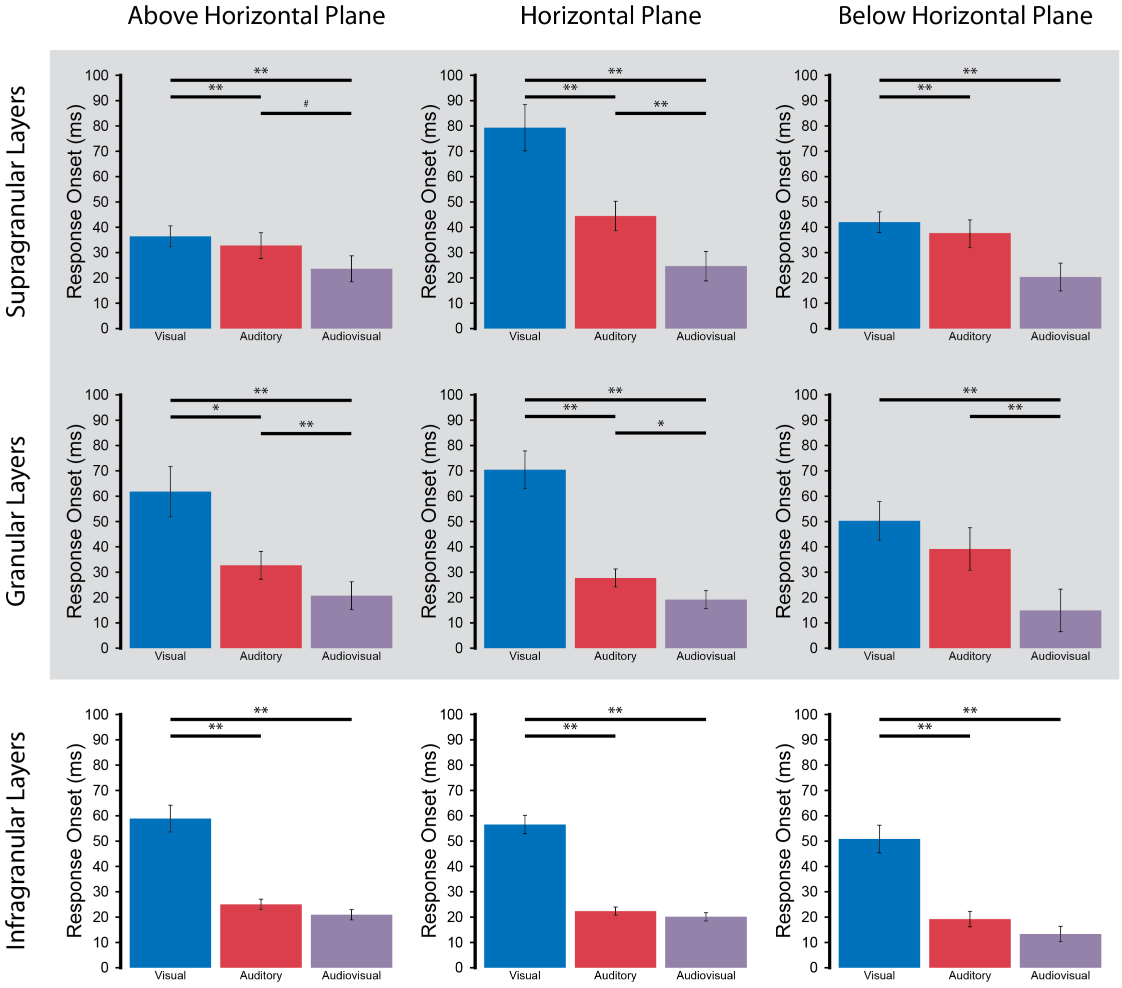


Figure 3-6: AV latency interactions take place in layers I-IV for all tested locations. Visual response onsets were slowest for all tested locations across all layers while auditory response onsets were smallest in infragranular layers. AV latencies were significantly reduced in upper layers (SG and G) for all tested locations. Color conventions are V (blue), A (red), AV (purple), A+V (yellow). **p<0.01. Error bars are S.E.M.

Discussion

Evidence of multisensory processing in insular cortex is abundant in human studies (for a general review see (Nieuwenhuys, 2012)) but direct testing of multisensory interactions is scarce. Furthermore, although, bimodal and trimodal neurons have been identified, both in primates (Benevento et al., 1977; Grusser et al., 1990a, 1990b; Shinder & Newlands, 2014; Thorpe et al., 1983) and in cat (Benedek et al., 1996; Hicks et al., 1988a) and one study even described interactions in local field potentials (LFPs, (Hicks et al., 1988a), no thorough analysis of multisensory integration at the neural level in insula has been undertaken. The current study sought out to characterize audiovisual integration within a sensory subfield, the anterior sylvian area (AS), in cat insula. Multisensory integration was evaluated with varying stimulus locations and stimulus onset asynchronies, similarly to what has been done before to quantify multisensory integration in other brain structures (Carriere et al., 2008; Ghose & Wallace, 2014; Krueger et al., 2009; Meredith & Stein, 1983, 1986a; Meredith et al., 1987; Royal et al., 2009).

Briefly, interactions were observed during audiovisual stimulation with significant increases in peak amplitudes and response magnitudes compared to the maximum unisensory response and significant subadditive effects compared to the linear prediction. Some spatial-specificity of the signal was noted in preferential interactions for locations above and below the horizontal plane. Most strikingly however were significant decreases in response onset during audiovisual trials. Latency reductions were evident for stimulus pairs with short stimulus onset asynchronies (SOAs) while significant delays of onset were observed for multisensory trials with larger SOAs. Rectifying for SOA further elucidated response onset gains at all tested SOAs. Furthermore, these audiovisual interactions resulting in shorter latencies were restricted to upper layers yet showed no significant stimulus location preference.

As mentioned earlier, a single previous study mapped (multi)sensory interactions in cat insula in LFPs (Hicks et al., 1988a). Measuring both, single cell and local field potential activity, they illustrated that more than 80% of recording sites showed multisensory properties, although this often necessitated 'non-physiological' stimulation such as auditory clicks being much louder than what was required to drive a unisensory cell. In fact, the majority of unisensory neurons showed some bimodality when stimulation was increased past physiological levels. The present data show similar interactions (although we did not test physiological versus non-physiological stimulus levels) as seen in changes in peak amplitudes or response magnitudes (measures that Hicks and colleagues employed). Furthermore, we also examined changes in latencies as speeding up of response onsets has frequently been noted in other studies (Rowland & Stein, 2008; Royal et al., 2009). In addition to showing response latency shifts in general, an interesting circuit pattern emerged in line with insula's role in integrating internal and external cues as well as in motor-related behaviors (Nieuwenhuys, 2012).

AS has strong reciprocal connections with auditory, visual and other multisensory regions along the anterior ectosylvian, posterior ectosylvian, and suprasylvian sulci and gyri as well as motor areas, neighboring insular fields and thalamic nuclei (Clasca et al., 1997, 2000). In accordance with other anatomical and functional studies (Benevento & Loe, 1975; Bignall et al., 1966; Hicks et al., 1988a), Clasca and colleagues proposed AS to be part of a visuomotor loop involved in orientation behaviors. The current data extend this to include multisensory interactions. Some spatial-specificity was observed in audiovisual response magnitudes, which would support the notion of an insular role in orienting to relevant stimuli, in this case being multisensory in nature. Here, monitoring regions within the receptive field that show differential responses between unisensory and multisensory stimuli (for example by showing response enhancement during multisensory conditions) may be a mechanisms which allows a network to detect and keep track of relevant or salient stimuli. Indeed, studies of the superior colliculus, which is highly implicated in behaviors involving head, eye, and pinnae movements in cats and primates (McHaffie & Stein, 1982; Stein & Clamann, 1981; Stein et al., 1976; Stryker & Schiller, 1975; Wurtz & Goldberg, 1972), have demonstrated substantial multisensory convergence as one possible underlying mechanism or contributor to said behaviors (Cuppini et al., 2010; Harris et al., 1980; Jay & Sparks, 1984; Peck, 1987; Rowland, Stanford, et al., 2007a; Rowland, Stanford, et al., 2007b; Stein & Stanford, 2008) and improvements in orientating with multisensory stimuli have been noted in behavioral assessments (Stein et al., 1988). Furthermore, these studies have frequently proposed that multisensory stimuli may be more salient and thus easier to detect. Similar interactions have been observed in cortical regions of the parietal sulcus in primates, which deal with orientation behaviors as well as grasping and reaching (Avillac et al., 2007; Bremmer et al., 2002; Chen et al., 2011; Cohen, 2009; Duhamel et al., 1998; Grefkes & Fink, 2005; Schlack et al., 2005) suggesting that this may be a general processing strategy spanning subcortex and cortex. Additionally, research looking at human performance has also shown increased localization accuracies under multisensory conditions (Hairston, Laurienti, et al., 2003; Hairston, Wallace, et al., 2003).

A second noteworthy observation is that the current data showed significant decreases in response onsets. As alluded to in the introduction, multisensory behavioral gains often include reduced response times (RT, (Amlot et al., 2003; Bernstein et al., 1969; Hecht et al., 2008)). In order to accommodate speeding up of behaviors, neural processes presumably need to be faster as well. Insula’s connections to motor areas make it a prime candidate for mediating processes that could result in these decreased RTs. Faster neural signals indeed have been associated with faster RTs in a simple detection task, although it is unclear whether or not modulations in unisensory cortex or integration in association cortex facilitated this behavior (Molholm et al., 2002) but evidence suggests that cross-modal oscillatory phase resets may underlie this phenomena (Mercier et al., 2015). Although not tested in this study, audiovisual phase shifting at the level of LFPs may be one mechanism in the insula that could drive facilitation in RTs. Indeed, somatosensory and visual influences in primate auditory cortex have been illustrated to reset ongoing auditory activity in order to optimize processing of newly arriving signals (Lakatos et al., 2007; Schroeder & Foxe, 2005).

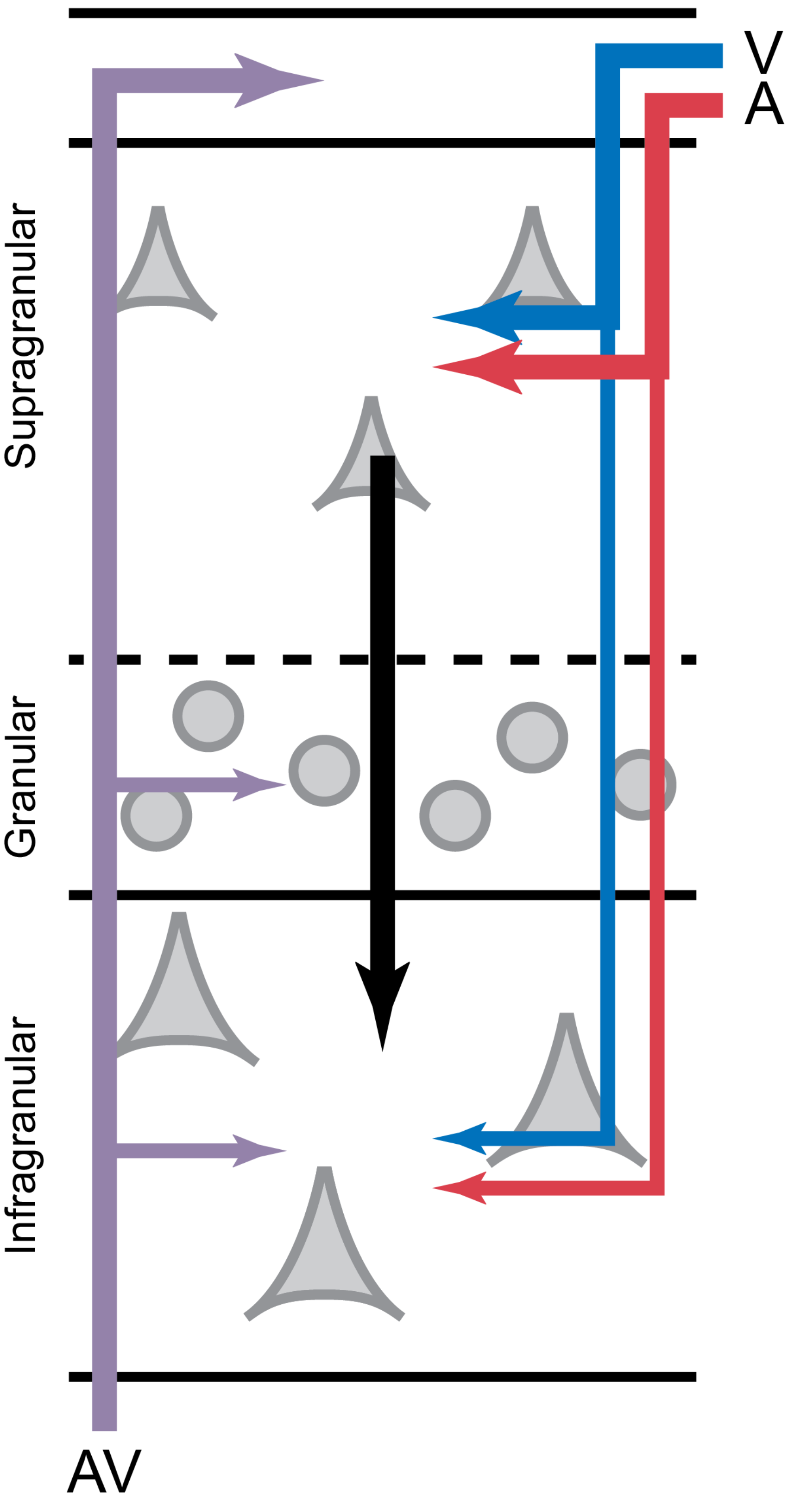

V
A
Supragranular
Granular
Infragranular
AV

Figure 3-7: Proposed model depicting auditory and visual cortical as well as thalamic influences on insular cortex. Color conventions are as follows; auditory – red, visual – blue, and multisensory – purple.

Insula involvement in (multi)sensory-motor mediation is further supported by the layer-specificity of multisensory interactions observed in the current study. Interestingly, response onset reductions here were restricted to upper cortical layers. Particularly, corticocortical interactions are thought to take place in supragranular layers as they are the recipient layers of other cortical inputs. Insula’s connections with unisensory and multisensory cortex supports this notion of corticocortical integration, although some thalamus involvement may be possible in layer I and IV. Indeed, the observed short latencies may hint at an involvement of thalamus nuclei such as the suprageniculate nucleus whereby multisensory transforms may already take place in said nucleus. Figure 3-7 depicts a proposed model of inputs supporting the observed interactions in the current data set. Further supporting (multi)sensory-mediations is that fact that the upper layers are also the presumed input layers from motor regions, which would allow for sensorimotor interactions. A large number of the aforementioned studies investigating multisensory integration and its contributions to orientation behaviors commonly feature strong connections between motor areas and the region of interest. AS in cat sends to and receives information from the dorsolateral and dorsomedial prefrontal sectors and (DIP and DmP, (Clasca et al., 2000)), which in conjunction with the frontal eye fields are implicated in visuomotor processing (Guitton & Mandl, 1978a, 1978b). And thus, it seems plausible then to postulate that insula may mediate multisensory-motor convergence, which in turn may lead to well-known behavioral benefits under multisensory integration such as higher accuracies in localizing stimuli or reduced response times during stimulus detection.

Altogether, the present study highlights the multisensory nature of insular cortex and delineates some spatial and temporal specificity of audiovisual interactions. Further studies are needed to evaluate the direct contributions of multisensory processing to behavior and perception but evidence suggests at least a role in sensorimotor convergence. Further functional implications may involve memory-related processes as insula also has strong reciprocal connections with perirhinal cortex (Clasca et al., 2000), although evaluation of these interactions were outside of the scope of the current experiment.

CHAPTER IV

VISUAL INFLUENCES IN CAT AUDITORY CORTEX: STIMULUS LOCATION SPECIFICITY AND LAMINAR DIFFERENCES OF THE SIGNAL

This chapter is a manuscript in preparation for submission to the 'Journal of Neurophysiology' as: Krueger Fister J, Nidiffer AR, Kurela LR, and Wallace MT. Visual influences in cat auditory cortex: stimulus location specificity and laminar differences of the signal.

Introduction

Introduction to multisensory processing

Many events in our daily environment are defined by stimuli from multiple senses. As a consequence of living in a multisensory world, our brain is tasked with integrating sensory cues from the different modalities in order to benefit behavior and create a unified perceptual reality. Indeed, having access to information from multiple sensory modalities has been shown to have many behavioral (speeded reaction times

(Amlot et al., 2003; Hairston et al., 2006), increased accuracies (Hairston, Laurienti, et al., 2003; Lovelace et al., 2003), and increased detection rates (Frassinetti et al., 2002)) and perceptual and cognitive (Calvert et al., 2004; Heed & Roder, 2012; Shams & Seitz, 2008; Soto-Faraco & Valjamae, 2012; Stein & Stanford, 2008) benefits. These benefits can be particularly striking when the component unisensory stimuli are ambiguous or weakly effective (Cappe et al., 2010; Nidiffer et al., 2015 (in revision); Stevenson, Bushmakin, et al., 2012). At the neural level various specialized brain regions that receive convergent input from multiple senses have been shown to actively integrate these sensory cues. Indeed, such multisensory brain regions are seen at multiple levels up and down the neuraxis, with a number of areas of the cerebral cortex being structured to carry out multisensory processing (for a review see (Stein & Stanford, 2008)).

Evidence for multisensory processing in primary cortices

In the traditional view of multisensory cortical organization, multisensory processing was thought to take place in higher-order or associational cortical areas after substantial unisensory processing has taken place within the relevant sensory cortices. However, recent evidence has called this model into question by detailing significant multisensory effects in areas traditionally deemed unisensory (Ghazanfar & Schroeder, 2006; Macaluso, 2006; Meredith et al., 2009; Musacchia & Schroeder, 2009; Schroeder & Foxe, 2005). For example, Schroeder and colleagues have investigated how somatosensory and visual signals influence auditory processing in core and belt regions of primate auditory cortex (Schroeder & Foxe, 2002; Schroeder, Lindsley, et al., 2001). Their data show influences from the non-dominant modality (i.e., somatosensation or vision) that amplify the processing of the dominant modality signal through mechanisms such as phase resetting of oscillatory activity (Lakatos et al., 2007). Kayser and colleagues have observed a similar phenomenon where vision has a strong influence over oscillatory patterns in auditory cortex (Kayser et al., 2008). In addition, investigations in primates and humans using methods to examine large ensemble population responses (i.e., EEG and fMRI) have also demonstrated non-auditory influences in auditory cortex (Calvert et al., 1997; Fort et al., 2002; Giard & Peronnet, 1999; Kayser et al., 2007; Murray et al., 2005; Pekkola et al., 2005). In a parallel manner, auditory signals have also been shown to influence early visual processing streams. For example, increased activity is seen in human occipital lobe during audiovisual stimulation (Molholm et al., 2002), decreased neuronal response latencies are seen in primate V1 during audiovisual stimulation (Wang et al., 2008), and cross-modal phase resetting by auditory influences has been illustrated in human visual cortices (Mercier et al., 2013; Naue et al., 2011). One possibility for these cross-modal influences in these so-called unisensory cortical domains is that the serve a generalized alerting function. However, countering this idea is the fact that these influences demonstrate a surprising degree of specificity. For instance, in ferrets Bizley and colleagues have shown that visual signals strongly influence auditory processing in a spatially-specific manner (Bizley & King, 2008, 2009). In addition to this physiological evidence, there is anatomical evidence in support of multisensory influences in domains traditionally considered unisensory (Bizley et al., 2007; Budinger & Scheich, 2009; Cappe & Barone, 2005; Cappe et al., 2009; Falchier et al., 2002; Falchier et al., 2010; Smiley & Falchier, 2009).

The purpose of this study

Despite a growing body of evidence illustrating the impact of multisensory influences in unisensory cortical domains, a number of open questions remain in regards to these interactions, particularly as they relate to the spatial and laminar specificity of the influences from the non-dominant modality. In the current study, we sought to address some of these open questions by examining visual influences on auditory processing in primary auditory cortex (AI) of the cat. Three major questions motivated the work: 1) are there visual influences in cat A1, as has been established in other species, 2) if so, do these visual influences on auditory processing differ based upon stimulus location (i.e., do they have a spatial specificity) as demonstrated by Bizley and colleagues in ferrets, and 3) if so, do these influences differ between supragranular, granular, and infragranular layers? Understanding how multisensory circuits are built is a crucial first step in evaluating multisensory interactions in the context of network activity and behavior and perception. Furthermore, identifying common patterns and differences across species as well as brain regions will aid in delineating multisensory processing strategies, which can comprise general features of multisensory integration as well as region- or function-specificity.

Methods

General procedures

The present study is part of a larger ongoing effort to delineate physiological and anatomical features of multisensory interactions in various regions in cat cortex and their contributions to multisensory network processing. Here, 3 adult cats underwent terminal extracellular recordings in primary auditory and surrounding cortex utilizing a 16 or 24 channel laminar U-probe (Plexon Inc). Data were collected during auditory, visual, and auditory-visual stimulation. All experiments took place under anesthesia and were performed in compliance with the *Guide for the Care and Use of Laboratory Animals* at Vanderbilt University Medical Center, which holds and accreditation by the American

Association for Accreditation of Laboratory Animal Care. At the end of the recording experiment, animals were euthanized and perfused.

Surgical Procedure

Initial anesthesia was accomplished via intramuscular injection of ketamine hydrochloride (20 mg/kg) and acepromazine maleate (0.04 mg/kg). Animals were promptly intubated and artificially respirated. Anesthesia throughout the surgical procedure occurred by inhalant isoflurane (<2%). The animal was then placed into a stereotax. The animal’s vital signs such as heart rate, respiration rate, expiratory CO2%, blood oxygenation levels, and body temperature were continuously tracked and recorded by a veterinary vital sign monitor ((VetSpecs monitor, VSM8 or a Scil monitor). After incision over the midline, tissue and muscle were retracted to expose the skull bone over temporal cortex. With the aid of the external suture lines of the bone, a craniotomy was made as so to expose primary and surrounding auditory cortex. In order to maintain a recumbent position during the recording portion of the experiment, a stainless steel chamber was placed over the midline atop the skull and anchored with surgical screws and dental cement. Once, the surgery was completed, the animal was switched to a ketamine (5 mg/kg/hr, IV) and vecuronium bromide (0.2mg/kg/hr, IV) or rocuronium bromide ([conc]) maintenance cocktail administered through the saphenous vein to maintain a stable plane of anesthesia. Neuromuscular blocking agents were added to the continuous infusion in order to ensure paralysis necessary to prevent ocular drift. SubQ fluids were provided throughout the entire experiment.

Mapping procedure

Single microelectrodes (parylene-insulated, tungsten, Z = 1.5-4 mΩ at 1 kHz) were advanced into primary auditory cortex and surrounding cortex in order to characterize physiological properties of the target region such as general responsiveness and stimulus preferences (auditory, visual, and auditory-visual) as well as to localize the borders of A1. Neural activity was amplified, recorded, and stored through a specialized Plexon 16 - 32 channel MAP system. When mapping was completed, a 16 or 24 channel laminar U-probe (channel spacing: 125 µm, distance from electrode tip to first channel: 700µm, Z = ~1mΩ) was advanced into primary auditory cortex. Care was taken to choose a recording depth that ensures channel distribution across all cortical layers (with channel 1 being always outside of the brain), which being conservative led to 2 – 3 different recording depths per recording location if necessary when using the 16 channel electrode. When multiple recording depths were needed, offline analysis of LFP latencies was utilized to match the channels.

Recording procedure

Once the U-probe was in place (recording depth of channel 24 at around 3200µm, auditory, visual and audiovisual stimuli were played in pseudorandom order across multiple azimuth and elevations within the receptive field of the sampled auditory cortex location. Stimuli were delivered via a customized stimulus hoop and were generated through a custom Labview (National Instruments) program. On the hoop, light-emitting diodes (LEDs) and speakers were mounted in spatially coincident locations every 10° (azimuth), which could be rotated along its axis at 10° (elevation) increments (Figure 4-1b). Due to the constraints of the table on which the cat was situated, stimuli could be presented from -40° to 90° elevation and -90° to 90° azimuth (see Figure 4-1). Visual stimuli were 100 ms single LED flashes (luminance 104 cd/m^2), presented to the contralateral eye to the recording electrode. The ipsilateral eye was occluded throughout recordings. Auditory stimuli consisted of 100 ms broadband noise bursts (20 Hz – 20 kHz, 67 dB SPL, background: 45 dB SPL). Inter-trial-intervals ranged from 2000 - 4000ms and each stimulus condition was presented 400 times. During multisensory trials, auditory and visual stimuli were always objectively simultaneous. Over the course of one experiment, 6-8 A1 locations were sampled.

Tracer injections

At the end of the experiment up to three small tracer injections were made in order to aid in reconstructing the tissue and to verify that recordings were actually made in primary auditory cortex. Immediately after tracer placement, the animal was euthanized and perfused with 4% PFA. The brain was then extracted from the skull and stored for 3 days in 30% sucrose. Sections surrounding auditory cortex were cut at 40µm with a microtome. Sections were visualized with a fluorescent Nikon i80 microscope/camera system and analyzed via custom software (Neurolucida).

Data analysis

Custom MATLAB scripts were used for all analysis. Recording files were imported into MATLAB and sorted by condition and channel. Multisensory mean voltages (average of the 400 trials per stimulus condition) were compared to the constituent unisensory voltages in multiple ways: peak/trough voltages (maximum peak after stimulus onset), peak/trough latencies and area under the curve (AUC) values for the first 500ms after stimulus onset. Peaks and troughs were only considered when the mean voltages exceeded a threshold, which was 2 standard deviations over baseline voltages (last 300ms before stimulus onset). For all relevant analyses, channel 1 voltages were removed from the data set as they were not reflective of brain activity (channel 1 was outside the brain to ensure optimal positioning of the Uprobe).

Generally, visual modulations were assessed by comparing auditory to audiovisual signals (amplitudes of peaks/troughs, peak/trough latencies, and overall response magnitudes). A variety of statistical tests were performed in order to do so and included two-tailed t-tests, Wilcoxon-sing-rank tests, repeated measures ANOVAs, as well as permutation tests. The time of use of each test is delineated in the results section.

For the cortical layer analysis, data were sorted by response onsets (LFP signal is above threshold (2 standard deviations over baseline voltages (last 300ms before stimulus onset)) for consecutive 15ms) in that latencies were calculated per channel and channels were matched to expected latencies for supragranular, granular, and infragranular layers. The data were then combined accordingly; which commonly resulted in channels 1-8 being considered to be located in supragranular layers, channels 9-12 in granular layers, and channels 13-24 in infragranular layers (and some in white matter).

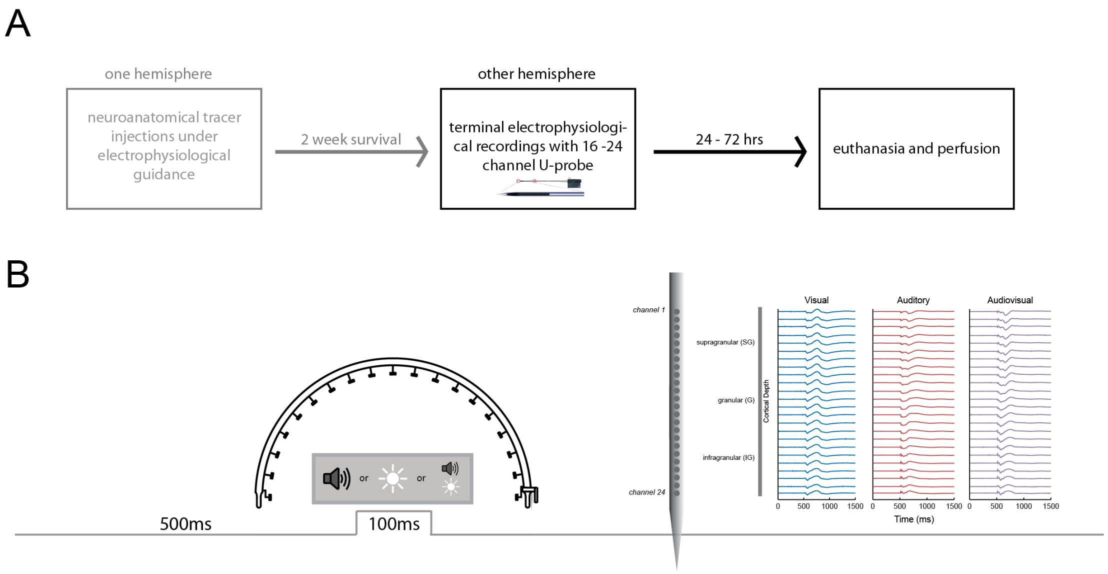


Figure 4-1: **A** – Experimental timeline. **B** – Recording trial structure with 500ms pre-stimulus interval, 100ms stimulus presentation, and then at least 1000ms post-stimulus interval. Stimuli included auditory only (A-red), visual only (V-blue), and audiovisual (AV-purple) at various locations (several azimuths and several elevations).

Results

Visual influences in primary auditory cortex (AI) are present in the local field potentials but not in spiking activity

The nature of the observed auditory (A) responses in AI in regards to latency, response magnitude and response duration were in keeping with those previously described in the literature. In contrast to the strong auditory responses seen in AI, visual stimuli failed to elicit spiking activity (Figure 4-2a). However, visual inputs into AI were evident in the LFP signal (Figure 4-2a and 4-2b, blue trace). In addition, although LFPs in response to combined audiovisual (AV) stimulation (Figure 4-2b, purple trace) often resembled those seen in response to auditory-only stimulation (Figure 4-2a and 4-2b, red trace), significant differences were seen between audiovisual, auditory and visual LFPs in peak amplitudes and latencies.

On account of these observed visual modulations of auditory LFPs, a set of analyses was undertaken to characterize the nature of these interactions. With our three main questions in mind, the first pass was to assess potential factors within the data indicative of multisensory interactions. This was followed by analyses looking at potential influences on the signal with varying stimulus locations. And thirdly, a layer-analysis was undertaken to delineate any differences between supragranular, granular, and infragranular laminae.

In order to gain insight if A1 shows multisensory interactions, a 4-way repeated measures ANOVA of the entire data set was employed to evaluate influences of stimulus modality (V, A, AV), stimulus location (azimuth, elevation), and recording channel (1-24). All (elevation, modality, recording channel) but one (azimuth) were found to be significant ($p_{(elevation)} = 0.003$; $p_{(modality)} = 0.0$; $p_{(channel)} < 0.01$; $p_{(azimuth)} = 0.5901$). This preliminary evidence was followed with more detailed analyses looking at common signal features that have shown integrative properties and findings will be discussed in subsequent sections.

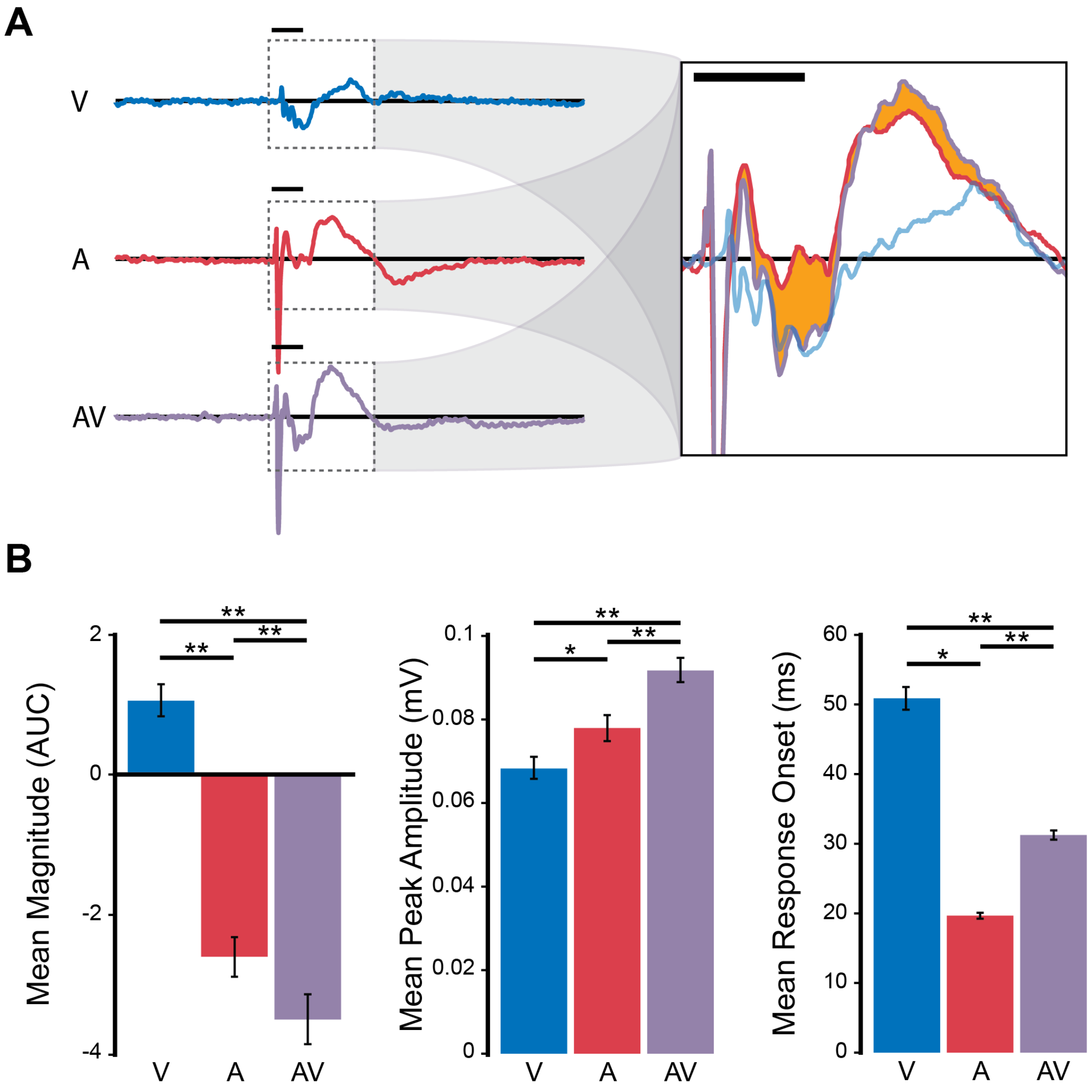


Figure 4-2: Visual influences on auditory processing. **A** – mean auditory local field potential (LFP) over time for each condition. Inset: shaded area (orange) shows difference between auditory and audiovisual LFP. Bar above each panel indicates stimulus timing. Prestimulus interval is 500ms. Stimulus duration is 100ms. **B** – Population mean magnitudes, mean peak amplitudes, and mean response onsets for all three conditions. Color conventions are blue for visual, red for auditory, and purple for audiovisual for all graphs. ** denotes $p < 0.01$.

Visual influences modulate auditory responses in primary auditory cortex

Since the ANOVA indicated potential audiovisual interactions, mean magnitude and mean peak changes in the LFP evaluated next. We based these measures on findings from prior work of other labs in primates showing visual modulations in AI to occur fairly late in the LFP signal (Schroeder & Foxe, 2002), and affecting LFP peak/trough amplitudes and peak latencies (Ghazanfar et al., 2005). In our data set, visual influences were indeed evident in changes in the mean magnitude of the LFP signal (defined as the area under the curve for the first 500ms after stimulus onset, Figure 4-2c left panel) when comparing audiovisual to auditory alone conditions, and in LFP mean and median peaks (Figure 4-2c right panel, Figure 3a and c). Wilcoxon-sign-rank tests revealed visual magnitudes (Table 4-1, Figure 4-2c left panel) and peak amplitudes (Table 4-1, Figure 4-2c right panel, Figure 4-3c right panel) to be significantly different from auditory and audiovisual magnitudes ($p_{(magnitude)} = 1{,}29 \times 10^{-36}$, $p_{(magnitude)} = 1.91 \times 10^{-66}$) and peak amplitudes ($p_{(peak\ amplitude)} = 2.56 \times 10^{-8}$, $p_{(peak\ amplitude)} = 4.53 \times 10^{-30}$). Additionally, auditory magnitudes and peaks and audiovisual magnitudes and peaks differed significantly from each other ($p_{(magnitude)} = 3.3 \times 10^{-23}$, $p_{(peak\ amplitude)} = 1.9 \times 10^{-44}$).

Prior work examining the temporal dynamics of multisensory integration suggests that most of the multisensory-mediated effects on spiking responses occur early in the response profile (Ghose et al., 2012; Rowland & Stein, 2008, 2014; Royal et al., 2009). Thus, response timings were evaluated for all three conditions. Two measures were employed – response onsets and peak latencies – in order to capture potential interactions. Response onsets (defined as a sustained response above threshold for consecutive 15ms) were found to be significantly different between conditions (A vs. V $p_{(response\ onset)} = 3.82 \times 10^{-81}$; A vs. AV $p_{(response\ onset)} = 3.12 \times 10^{-87}$; V vs. AV $p_{(response\ onset)} = 2.30 \times 10^{-38}$) with auditory onsets being the earliest onsets followed by audiovisual and then by visual signals (Table 1, Figure 4-2c). Furthermore, AV peak latencies (Figure 4-3c left panel) were significantly slower than A ($p_{(peak\ latency)} = 3.27 \times 10^{-6}$) and significantly faster than V ($p_{(peak\ latency)} = 1.98 \times 10^{-29}$) latencies. A and V latencies were also significantly different from each other ($p_{(peak\ latency)} = 6.39 \times 10^{-34}$).

Table 1: Mean response magnitudes, peak amplitudes, and response onsets for all conditions

	Visual	Auditory	Audiovisual
Response magnitude (AU)	1.068 +- 0.223	-2.606 +- 0.294	-3.508 +- 0.355
Peak amplitude (mV)	0.068 +- 0.003	0.078 +- 0.003	0.092 +- 0.003
Response onset (ms)	50.88 +- 1.63	19.5 +- 0.42	31.14 +- 0.66

Table 4-1: Summary of local field potential measures per condition.

Early and late visual influences on ongoing auditory activity

Multisensory interactions observed in spikes show that increase in spikes are frequently associated with a decrease in response latency (Rowland & Stein, 2008; Royal et al., 2009). In order to delineate the timing of the visual modulations on auditory LFP responses in AI, and to investigate if changes in the timing of responses are associated with change in the magnitude (i.e., gain) of the responses, the latency of the peaks of the LFP signals were plotted against the amplitude of these signals for auditory, visual and combined audiovisual conditions (Figure 4-3a, circles denote median latencies and standard error means (SEMs)). Peak amplitudes and latencies were chosen over response magnitudes and onsets as they are a more reliable and accurate measure given that they occur at a specific time point over the span of the LFP signal.

Two distinct populations were evident in the peak latency of the LFP responses (Figure 4-3a). As a consequence, early (less than 100 ms) and late (100ms to 500 ms) peak latencies were evaluated separately. Permutation tests (10000 repeats, no replacement, Figure 4-3a inset) unmasked that AV signals peak significantly later than auditory signals ($p_{(\text{early peak latency})} = 0.0069$) in the early cluster and significantly earlier ($p_{(\text{late peak latency})} < 1 \times 10^{-4}$) in the late cluster while both showed increased AV peak amplitudes ($p_{(\text{early peak amplitude})} < 1 \times 10^{-4}$; $p_{(\text{late peak amplitude})} < 1 \times 10^{-4}$).

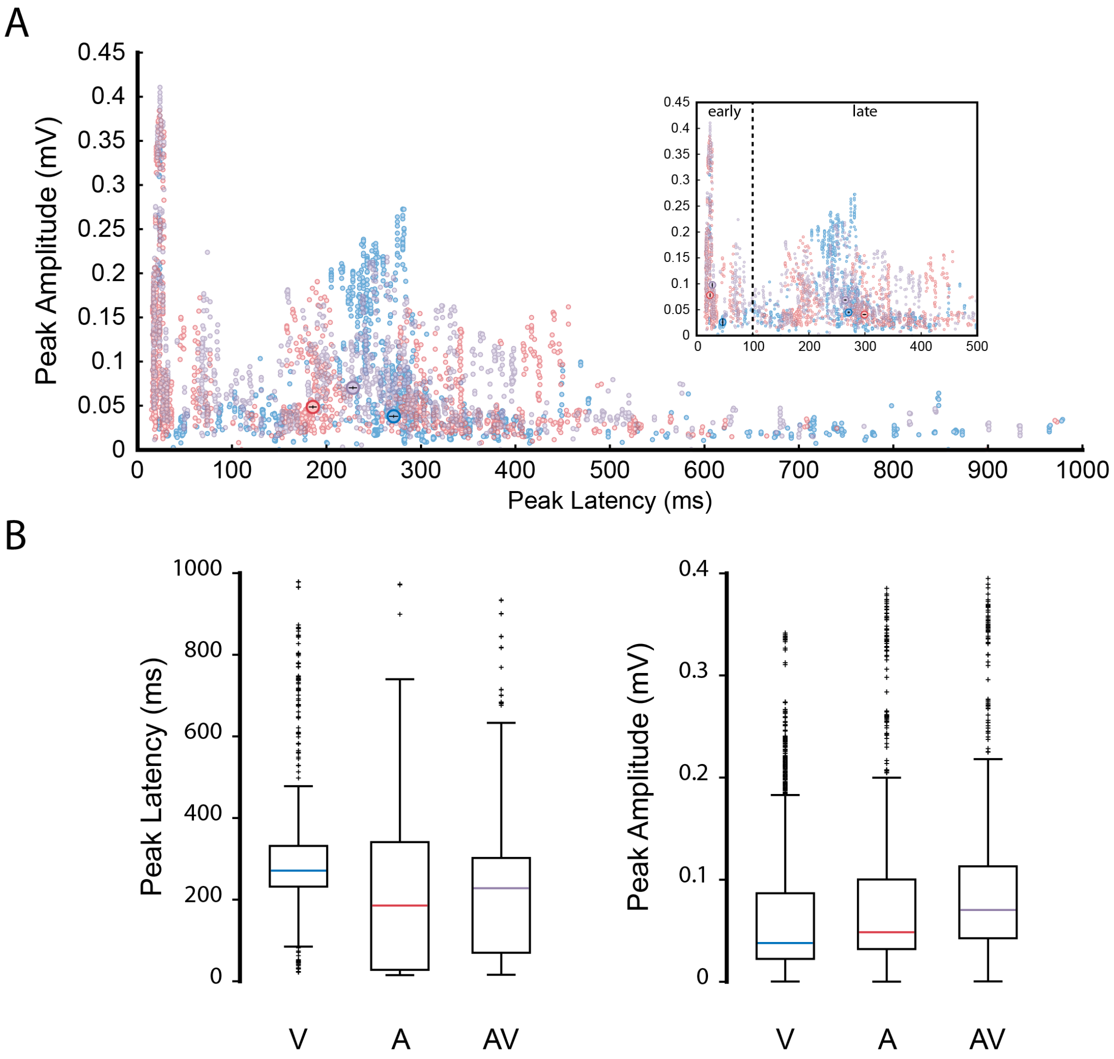


Figure 4-3: **A** – Peak latency versus amplitude scatterplots (circles denote median latencies and SEMs). Inset in panel shows median and SEM values for early and late latency clusters. **B** – Boxplots for peak amplitudes and latencies. Color conventions are blue for visual, red for auditory, and purple for audiovisual for all graphs.

Auditory activity is modulated by visual signals in a spatially-dependent manner

As described earlier, a repeated measures ANOVA on the LFP signals revealed that they differed dependent upon the spatial location of the stimuli, with these differences only present for changes in the dimension of elevation. To further evaluate these elevation-dependent influences, LFP peak amplitudes (Figures 4-4, 4-5, and 4-6) and latencies (Figure 4-7) were collapsed across azimuth for each stimulus condition. Figure 4-4 depicts mean peak amplitude changes for A, V and AV LFPs for locations in superior (i.e., above the interaural plane) space (left panels), for locations along the interaural plane (middle panels), and for locations in inferior (i.e., below the horizontal plane) space (right panels). Notably, audiovisual peak amplitudes (Figure 4-4a) were significantly larger than auditory peak amplitudes for all locations except for the horizontal plane ($p_{(\text{above horizontal plane})} = 3.13 \times 10^{-7}$; $p_{(\text{below horizontal plane})} = 2.58 \times 10^{-7}$; $p_{(\text{horizontal plane})} = 0.5353$). Intriguingly, these locations (Figure 4-4b) were also the locations at which the magnitude of the auditory LFP peaks were smallest ($p_{(\text{above horizontal plane})} = 1.79 \times 10^{-4}$; $p_{(\text{below horizontal plane})} = 1.55 \times 10^{-12}$) and the magnitude of the visual peaks were strongest ($p_{(\text{above horizontal plane})} = 5.18 \times 10^{-27}$; $p_{(\text{below horizontal plane})} = 4.5 \times 10^{-11}$).

Auditory and audiovisual LFPs differ in a layer specific manner

Analysis of the population data revealed that visual peak amplitudes did not greatly differ between the cortical layers (Figure 4-5 left panel) indicative of potentially broad influences across the various cortical laminae. In contrast, auditory peak amplitudes (Figure 4-5 middle panel) were significantly larger in supragranular ($p = 1.71 \times 10^{-4}$) and infragranular layers ($p = 0.002$) compared to the granular layer. This also held true for audiovisual peak amplitudes (Figure 4-5b right panel, $p = 0.007$; $p = 0.007$, respectively).

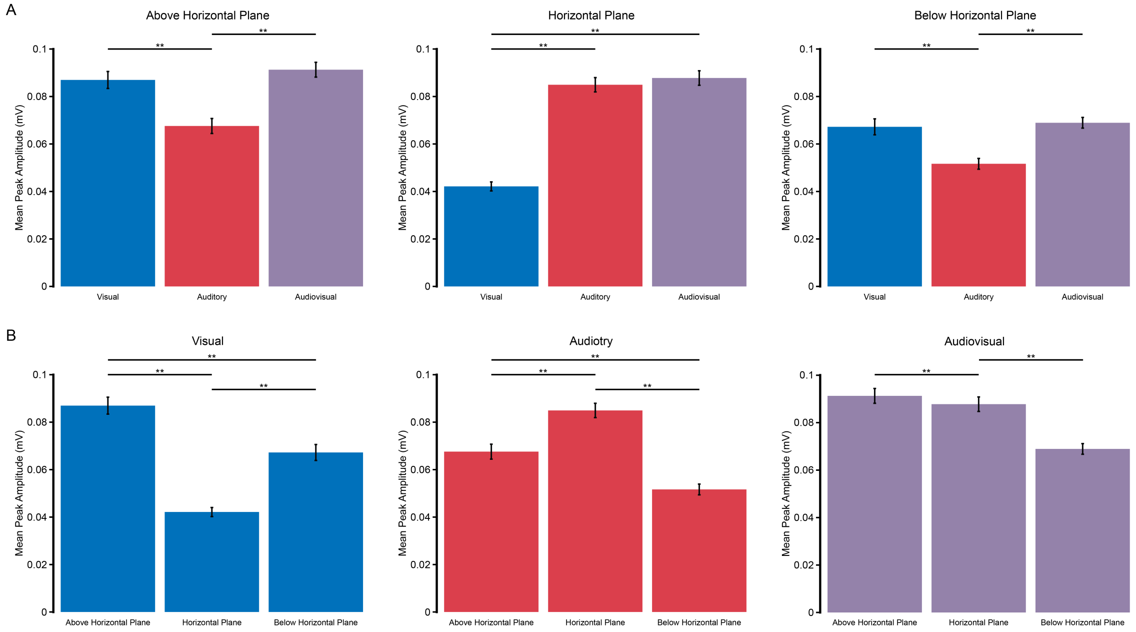


Figure 4-4: Population data depicting mean peak amplitudes across all conditions by elevation. **A** – Peak amplitude comparisons across conditions. **B** – Peak amplitude comparisons within conditions. Color conventions are blue for visual, red for auditory, and purple for audiovisual for all graphs. ** denotes $p < 0.01$.

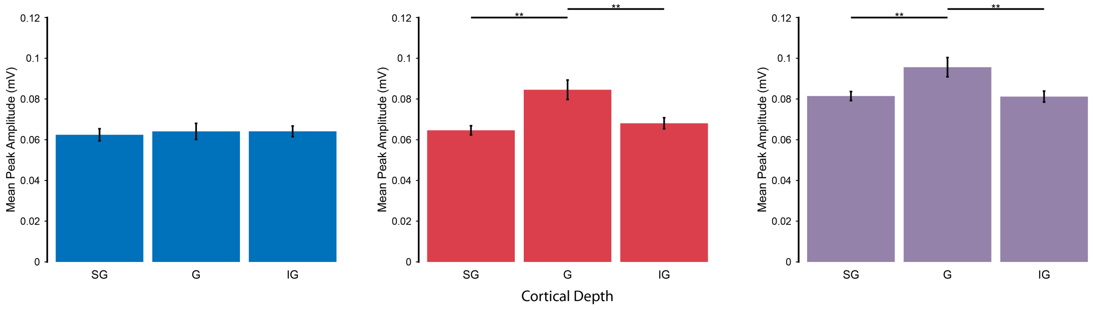


Figure 4-5: Mean peak amplitudes across cortical layers per condition. Color conventions are blue for visual, red for auditory, and purple for audiovisual. ** denotes $p < 0.01$.

Since the repeated measures ANOVA did not reveal significant effects for azimuth, stimulus location analysis was focused on elevation only. When collapsing across azimuths to look at the effects of stimulus elevation by layer (Figure 4-6), it became apparent that neither supragranular (SG), granular (G), nor infragranular (IG) layers showed any visual modulations of the auditory signal for horizontal plane stimulus locations (Figure 4-6b). For these locations along the interaural plane, visual mean LFP peaks were always significantly smaller than those for auditory stimuli ($p_{(SG)}$ = 1.31 X 10^{-6}; $p_{(G)}$ = 7.68 x 10^{-8}; $p_{(IG)}$ = 9.11 x 10^{-17}), suggesting that auditory signals may be particularly effective in driving responses in the interaural plane. In contrast, strong effects were observed outside the interaural plane (Figure 4-6a and 4-6c). Supragranular and infragranular layers exhibited significant differences in A and AV mean peak amplitudes for both superior ($p_{(SG)}$ = 3.48 x 10^{-4}; $p_{(IG)}$ = 1.28 x 10^{-4}) and inferior ($p_{(SG)}$ = 4.05 x 10^{-4}; $p_{(IG)}$ = 3.42 X 10^{-5}) locations. Visual mean peak amplitudes differed in SG layers for stimulus locations above and in the horizontal plane (p = 4.05 X10-5), and in IG layers for stimulus locations above and in the horizontal plane (p = 1.83 x 10^{-5}) as well as for stimulus locations below and in the horizontal plane (p = 4.78 x 10^{-5}).

In addition to peak amplitudes, peak latencies were also evaluated separated by layer in order to characterize potential differences between laminae for latency-stimulus location interactions. While significant latency differences between visual and auditory signals were present for all tested stimulus locations ($p<0.01$), significant latency shifts for AV conditions were only found in granular layers for stimuli located in the horizontal plane. Interestingly, this latency shift significantly delayed the audiovisual peak compared to the auditory peak ($p_{(\text{peak latency})}$ = 0.011). Nevertheless, collectively, these results suggest a strong spatial specificity for the visual modulatory influences on auditory responses.

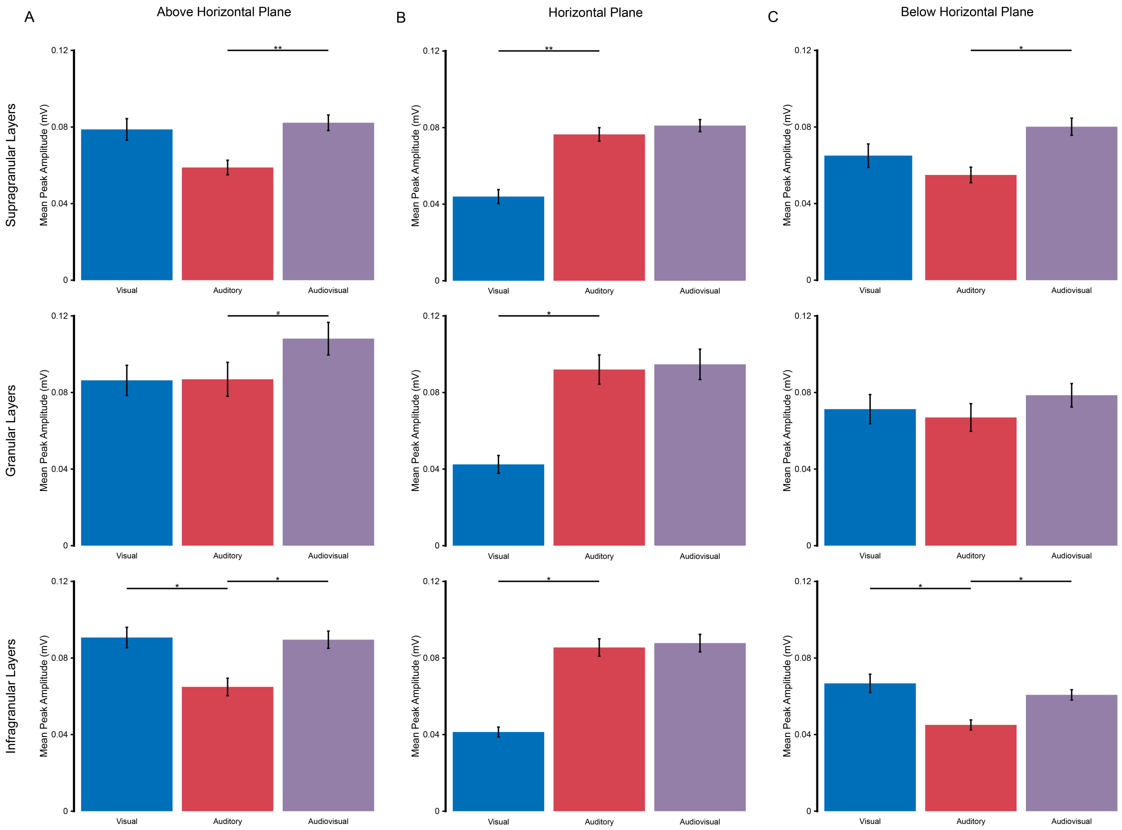


Figure 4-6: Population data depicting mean peaks across all conditions separated by cortical layers and by stimulus elevation (panel **A** – above horizontal plane, panel **B** – horizontal plane, panel **C** – below horizontal plane). Significant differences between A and AV peaks were observed for elevations above and below the horizontal plane. Color conventions are blue for visual, red for auditory, and purple for audiovisual for all graphs. ** denotes $p < 0.01$.

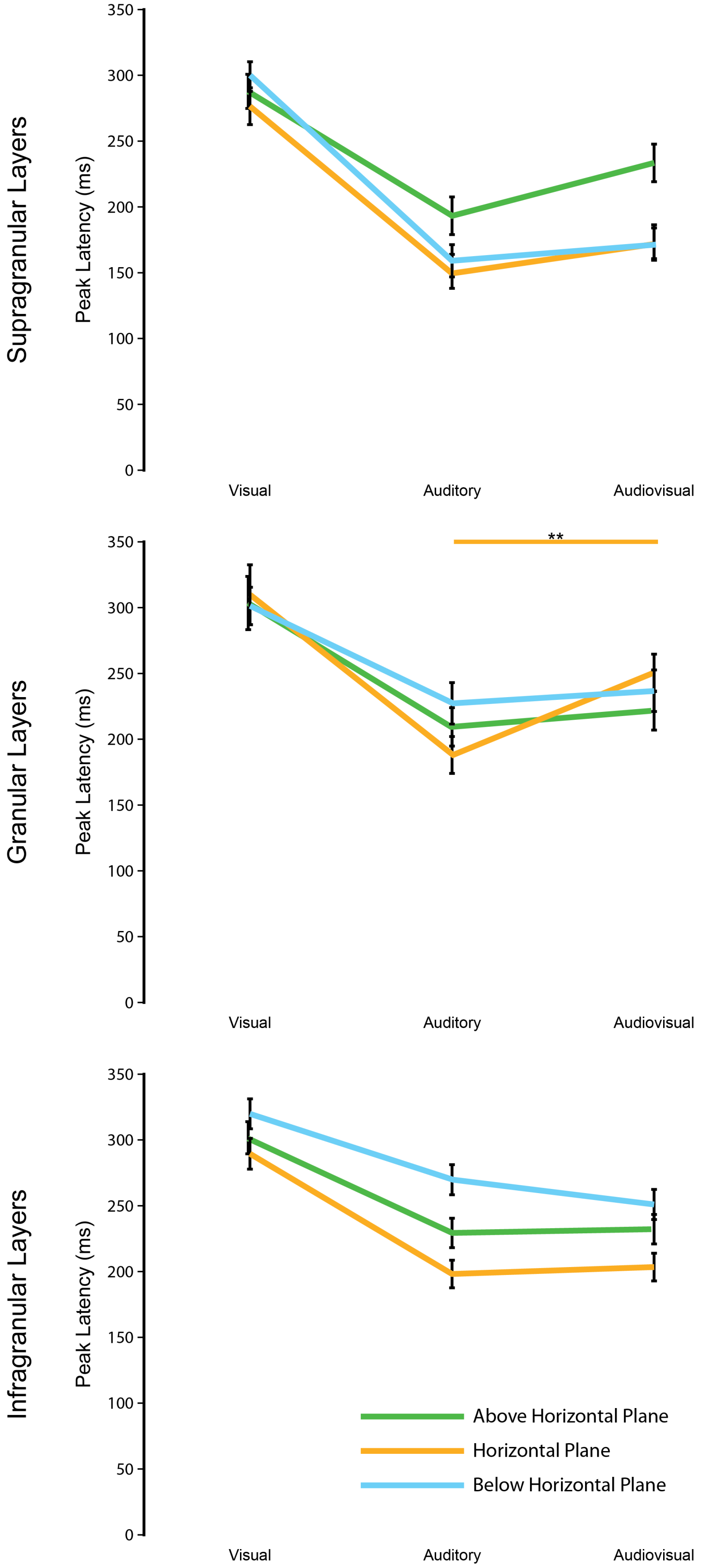

Supragranular Layers
Peak Latency (ms)
350
300
250
200
150
100
50
0
Visual
Auditory
Audiovisual
Granular Layers
Peak Latency (ms)
**
350
300
250
200
150
100
50
0
Visual
Auditory
Audiovisual
Infragranular Layers
Peak Latency (ms)
350
300
250
200
150
100
50
0
Visual
Auditory
Audiovisual
Above Horizontal Plane
Horizontal Plane
Below Horizontal Plane

Figure 4-7: Population data depicting mean peak latencies across all conditions separated by cortical layers and by stimulus elevation. Significant differences between A and AV peak latencies were only observed for stimuli located in the horizontal plane. Color conventions are green for locations above the horizontal plane, orange for locations in the horizontal plane, and blue for locations below the horizontal plane. ** denotes $p < 0.01$.

Discussion

As described in other species, auditory responses in cat primary auditory cortex are subject to visual modulation. In general, these visual influences manifest as enhancements in the magnitude of the LFP signal (when comparing audiovisual and auditory conditions) and in shifts in the latency of these signals. Similar findings have been described in primates (Cahill et al., 1996; Ghazanfar et al., 2005; Lakatos et al., 2007), rodents (Bizley & King, 2008; Cahill et al., 1996), and humans (Molholm et al., 2002; Murray et al., 2005). These visual influences appear to take place at both early and late periods of the evoked LFP, a finding congruent with what has been noted for both LFPs sampled from primate auditory cortex (Schroeder & Foxe, 2002) and spiking activity in cat SC (Ghose et al., 2012; Royal et al., 2009). Furthermore, the present data reveal a spatial specificity to these influences (Bizley & King, 2008, 2009), as well as effects that are in keeping with the principle of inverse effectiveness and in which the visual influences were strongest when auditory evoked responses were weak (Meredith & Stein, 1983; Stein & Stanford, 2008; Wallace, Meredith, & Stein, 1992). This finding makes good ecological sense in illustrating that visual signals may be the most beneficial to the auditory system when auditory alone signals are weak or ambiguous (for an overview of multisensory gains under those conditions see (*The neural bases of multisensory processes*, 2012; Stein & Stanford, 2008).

Behaviorally, psychophysical experiments have illustrated that subjects are more accurate when asked to detect a specific stimulus (i.e. visual) with the addition of another stimulus cue (i.e. auditory), especially when the primary cue was degraded (Hairston, Laurienti, et al., 2003) or moved outside the horizontal midline (Hairston, Wallace, et al., 2003). The present data support such a notion as auditory peak values were selectively modulated with spatially-coincident, non-central visual stimuli; a phenomenon reinforced by anatomical and physiological data in other species

(Ghazanfar & Schroeder, 2006; Hackett & Schroeder, 2009; Schroeder et al., 2003). In further support of visual signals providing spatial information are the results of a laminar analysis. Here, although visual LFPs were evident across all of the cortical layers, visual peaks for stimuli above and below the horizontal plane were different in supragranular and infragranular layers from the granular layer. These findings of spatial specificity are in line with work from other labs (Bizley & King, 2008, 2009; Kayser et al., 2008) and suggest that visual modulations of ongoing auditory activity may provide contextual spatial information of multisensory event. Visual modulations in auditory cortex may further highlight a potential neural substrate to behavioral benefits such as increased accuracies in auditory localization tasks.

Prior work has also suggested that visual influences into AI are of a feedback nature (Ghazanfar & Schroeder, 2006; Schroeder & Foxe, 2002), but findings from this study (and others (Bizley et al., 2007; Giard & Peronnet, 1999; Lakatos et al., 2007; Molholm et al., 2002; Schroeder & Foxe, 2002) suggest that changes in the amplitude of the LFP signals occur much earlier than would be predicted if these were a result of feedback projections. Later changes are also seen in the LFP and that are suggestive of feedback, creating a scenario in which there may be both early feedforward modulations as well as later feedback influences. Indeed, anatomical studies in rodents (for a review see(Budinger & Scheich, 2009)) have shown inputs from lateral geniculate nucleus (LGN) across all layers in A1 that could support early interactions. In cat, no such connections with LGN have been demonstrated, but a few other thalamic nuclei may mediate such interactions, which will be further discussed in subsequent sections. Later integration may result from higher-order feedback projections arising from extrastriate visual regions and/or multisensory regions (for a review see (Smiley & Falchier, 2009)). Although the source(s) of these visual influences into AI in cat remain unknown, several possibilities exist. Prior work has shown that projections from the dorsal and medial division of the medial geniculate nucleus may already carry visual information (Wepsic, 1966; Winer & Lee, 2007), and thus could be influencing ongoing auditory activity in A1 in a feedforward manner. Projections from insula, and auditory association regions such as posterior ectosylvian regions (Lee & Winer, 2008a), which have been shown to have multisensory properties, could be the source of feedback projections. Figure 4-8 depicts a proposed circuit model highlighting differential inputs whereby both cortex as well as thalamus may modulate ongoing auditory activity. Corticocortical interactions are supported by audiovisual peak modulations in supra- and infragranular layers omitting layer IV and by latency shifts at times in the signal that would be expected for cortical visual (or multisensory) inputs (i.e. late peak latency interactions). Influences mediated by thalamus are evident in latency modulations early in the signal as well as latency delays restricted to layer IV. The delays further suggest that some multisensory transform may already take place at the level of thalamus rather than in auditory cortex. Collectively, this suggests a multi-faceted interplay between cortex and thalamus as well as between feedforward and feedback processes.

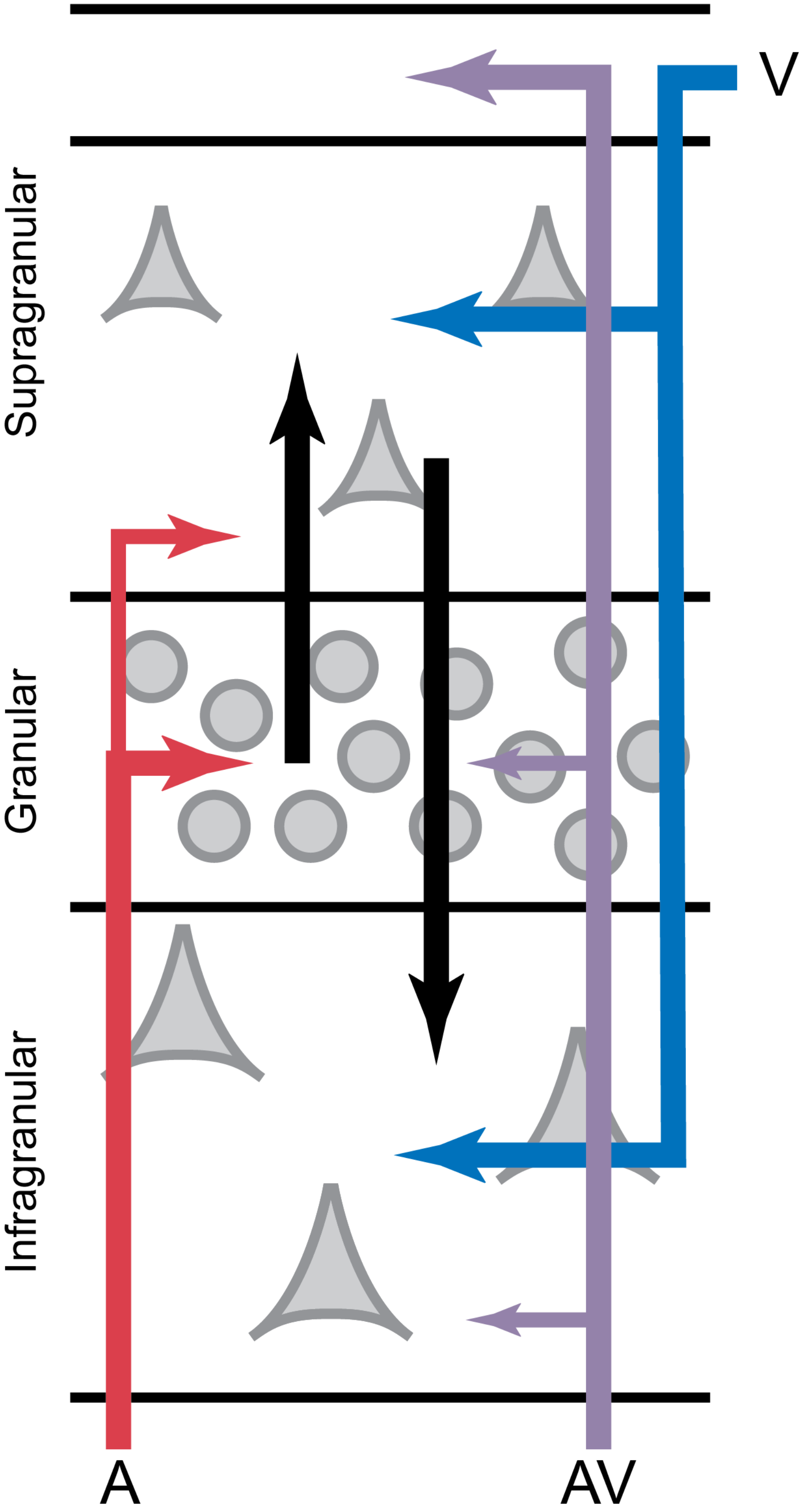

V
Supragranular
Granular
Infragranular
A
AV

Figure 4-8: Proposed model depicting visual or multisensory cortical as well as thalamic influences on auditory cortex. Color conventions are as follows; auditory – red, visual – blue, and multisensory – purple.

The exact contributions of these differential interactions remain to be elucidate but data from primates support both feedforward and feedback modulations (Schroeder & Foxe, 2002). Common mechanisms between these may involve neural oscillations. Indeed, somatosensory and visual activities in auditory cortex have been demonstrated to reset the phase of ongoing auditory oscillations (Lakatos et al., 2007; Schroeder & Foxe, 2002) thereby optimizing conditions for subsequently arriving LFP signals. Such a mechanisms could be at play during the current observed audiovisual interactions in cat cortex, but such analysis may be questionable with the present experimental design as it includes anesthesia. Thus, in order to elucidate other ways within which non-dominant modalities can influence cat A1 activity, looking at oscillatory patterns may be beneficial. Furthermore, a focused study on parceling out the contributions of feedforward and feedback visual influences may provide important mechanistic insight and may further our understanding of a neural substrate of the observed behavioral facilitations such as reduced reaction times and increased accuracies with the addition of a non-dominant stimulus.

CHAPTER V

SPATIAL RECEPTIVE FIELD ORGANIZATION OF MULTISENSORY NEURONS AND ITS IMPACT ON MULTISENSORY INTERACTIONS

This paper is published in the journal 'Hearing Research' as Krueger J, Royal DW, Fister MC, and Wallace MT (2009). Spatial receptive field organization of multisensory neurons and its impact on multisensory integration.

Abstract

Previous work has established that the spatial receptive fields (SRFs) of multisensory neurons in the cerebral cortex are strikingly heterogeneous, and that SRF architecture plays an important deterministic role in sensory responsiveness and multisensory integrative capacities. The initial part of this contribution serves to review these findings detailing the key features of SRF organization in cortical multisensory populations by highlighting work from the cat anterior ectosylvian sulcus (AES). In addition, we have recently conducted parallel studies designed to examine SRF architecture in the classic model for multi- sensory studies, the cat superior colliculus (SC), and we present some of the preliminary observations from the SC here. An examination of individual SC neurons revealed marked similarities between their

unisensory (i.e., visual and auditory) SRFs, as well as between these unisensory SRFs and the multisensory SRF. Despite these similarities within individual neurons, different SC neurons had SRFs that ranged from a single area of greatest activation (hot spot) to multiple and spatially discrete hot spots. Similar to cortical multisensory neurons, the interactive profile of SC neurons was correlated strongly to SRF architecture, closely following the principle of inverse effectiveness. Thus, large and often superadditive multisensory response enhancements were typically seen at SRF locations where visual and auditory stimuli were weakly effective. Conversely, subadditive interactions were seen at SRF locations where stimuli were highly effective. Despite the unique functions characteristic of cortical and subcortical multisensory circuits, our results suggest a strong mechanistic interrelationship between SRF microarchitecture and integrative capacity.

An introduction to multisensory interactions

Our environment is comprised of myriad sensory cues that are constantly changing along numerous dimensions (e.g., space, effectiveness, etc.). As a consequence of the dynamic nature of our sensory world, the nervous system is continually challenged with resolving the inherent ambiguities that result from these competing stimulus complexes in order to generate directed action and create veridical percepts. To accomplish this task, the brain has to correctly identify whether sensory energies propagated in different domains (e.g., light, sound, etc.) belong to a single event or are derived from several discrete events. Specialized structures, including the midbrain superior colliculus (SC), have evolved to process cues from multiple sensory systems and ultimately integrate this information into a meaningful construct. Indeed, the SC has been the classic model for physiological studies aimed at better elucidating the neurophysiological principles by which individual neurons integrate multisensory cues

(Meredith & Stein, 1986a, 1986b; Meredith et al., 1987; Wallace et al., 1992). The strength of the SC as a model has come from its well-established role in sensorimotor transformation (Sparks, 1986), its highly stereotyped spatiotopic and motor organization (Meredith & Stein, 1990; Meredith et al., 1991; Middlebrooks & Knudsen, 1984; Robinson, 1972; Stein et al., 1976), and the fact that a large percentage of its deep layer neurons receive convergent input from multiple modalities (Meredith et al., 1992; Wallace et al., 1993). In fact, a large body of work now exists which details the operational ‘‘principles” by which SC neurons synthesize their different multisensory inputs. These studies have highlighted the importance of space, time and stimulus effectiveness in dictating the product of a given multisensory combination. Although these studies have focused on parametric manipulation of one of these properties at a time (e.g., varying the spatial relationship of a multisensory stimulus pairing while keeping their temporal relationship and intensity constant), recent work has suggested a strong interdependence between these factors; an interdependence that more closely mimics the nature of a real world multisensory stimulus complex (Carriere et al., 2008; Royal et al., 2009).

These studies suggesting this interrelationship were motivated by observations that changes in the spatial position of stimuli within the excitatory receptive field resulted in dramatic changes in the response profile of the neuron. A more systematic analysis of this revealed that multisensory neurons are characterized by a complex spatial receptive field (SRF) architecture for each of the modalities to which they are responsive. Furthermore, this work showed that this SRF organization plays an important role in the integrative capacity of the studied neuron, specifically by modulating stimulus effectiveness in a spatially dependent manner.

The need for a comparison between cortical and subcortical multisensory circuits

Although these observations have provided new insights into the dynamism that characterizes multisensory neurons and their integrative properties, it must be reinforced that the majority of the work carried out to date has been in a cortical domain, the anterior ectosylvian sulcus (AES) of the cat. Given that the receptive fields of AES multisensory neurons are substantially larger than those in the SC (Wallace et al., 1992; Wallace et al., 2006), and that the visual and auditory representations in the AES are not spatiotopically ordered (Clarey & Irvine, 1990b; Olson & Graybiel, 1987), whether its SRF structure and its integrative consequences generalize to other multisensory structures remains unknown. This is particularly germane given the functional differences that undoubtedly exist between cortical and subcortical multisensory representations, with the former likely to play an important role in multisensory perceptual processes and the latter a larger role in stimulus- directed action (i.e., orientation). Hence, a comparison of cortical and subcortical multisensory populations in terms of their SRF organization and integrative features is likely to yield important insights into both the similarities and differences in the encoding of multisensory information used for perceptual and behavioral purposes. As a step in this process, here we seek to review the existing literature detailing cortical multisensory circuits and compare it with a preliminary data set taken from the SC.

Cortical multisensory neurons exhibit a complex spatial receptive field (SRF) organization

Single-unit recordings from the cortex of the cat anterior ectosylvian sulcus (AES) focused on defining the spatial receptive field architecture of multisensory neurons in this cortical region, and on examining how SRF structure impacted multisensory interactions in these neurons. The cat AES has become one of the predominant models for furthering our understanding of cortical multisensory processes, and is situated at the border between frontal, parietal and temporal cortices (Wallace et al., 1992). In addition to being comprised of three modality-specific representations, the anterior ectosylvian visual area (AEV; see (Benedek et al., 1988; Mucke et al., 1982; Norita et al., 1986)), the fourth somatosensory cortex (SIV; see (Clemo & Stein, 1982, 1983, 1984)), and the auditory field AES (FAES; see (Clarey & Irvine, 1986, 1990a, 1990b)), there is a substantial multisensory population that is located largely at the borders between these unisensory domains (Jiang et al., 1994a, 1994b; Wallace et al., 2006). Prior work has shown that the integrative features of these cortical multisensory neurons are very similar to those in the SC, in that these neurons have spatially-registered receptive fields and exhibit multisensory interactions that abide by the spatial, temporal and inverse effectiveness principles first delineated for the SC (Meredith & Stein, 1986a; Meredith et al., 1987; Stein & Wallace, 1996; Wallace et al., 1992).

The application of methods to define in more detail the receptive field organization of these AES multisensory neurons revealed a complex architecture to the individual unisensory receptive fields of these neurons. As opposed to prior approaches that had focused on defining the response borders of cortical (and subcortical) multisensory neurons, these new analyses sampled at numerous locations within these borders and created a higher resolution spatial receptive field (SRF; Figure 5-1). These SRF plots illustrated regions of vigorous response surrounded by regions of lesser response (note that the effectiveness of the stimuli used in these analyses was always identical) – a heterogeneity that had not been detailed in prior work (Figure 5-2). Of particular note was the fact that these SRFs could be comprised of singular or multiple hot spots of activity, and that the individual SRFs for the different effective modalities could be well-aligned or strikingly misaligned. The significance of this heterogeneity in both number and overlap remains to be determined

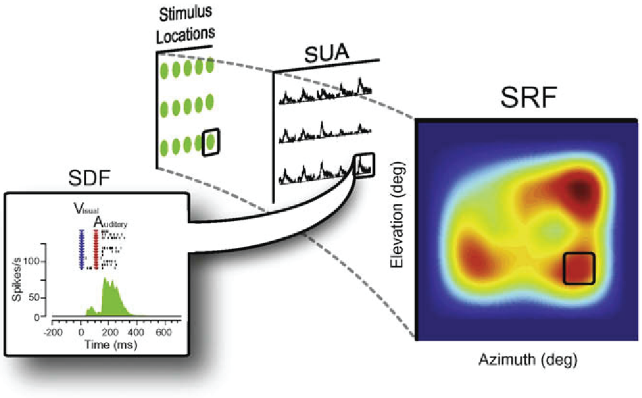


Figure 5-1: Method for constructing a spatial receptive field (SRF) for an individual SC neuron. Green circles represent the tested stimulus locations within the classical excitatory receptive field. Responses at each of these locations are then assembled into the single unit activity (SUA) plots. A single SUA plot at one location is enlarged to show how the spike density function (SDF) is derived. The SUA/SDF data are then transformed into the pseudocolor spatial receptive field (SRF) plot. In this plot the normalized evoked response (scaled to the maximal response) is shown as a function of azimuth (x-axis) and elevation (y-axis), with warmer colors representing higher firing rates.

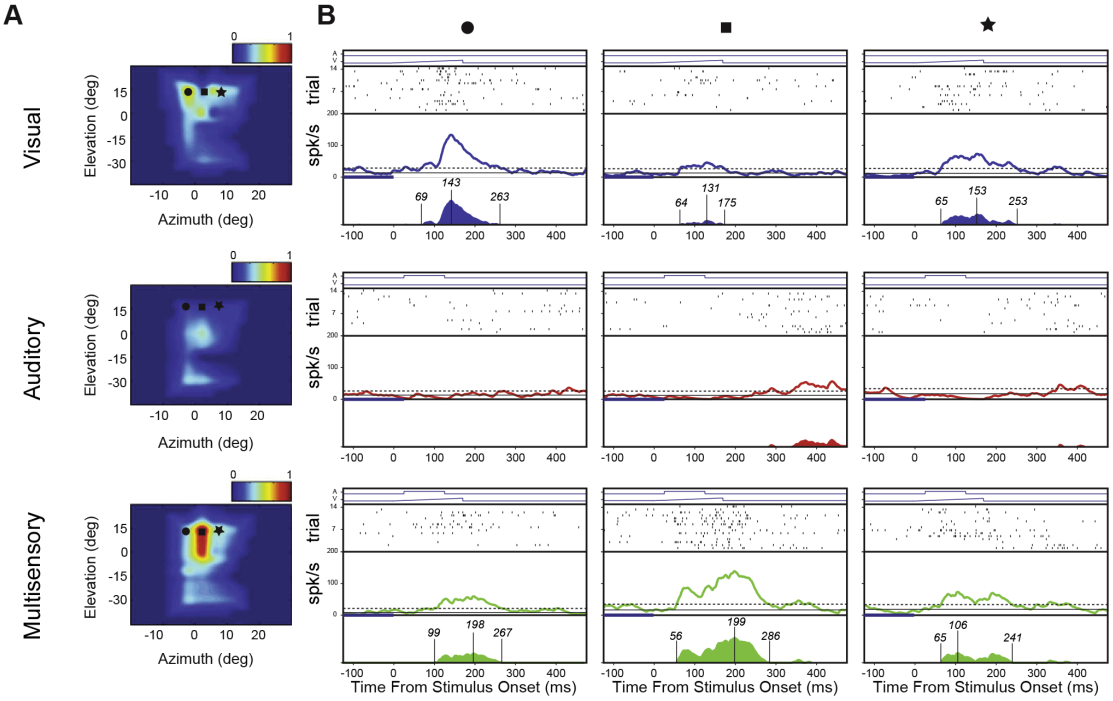


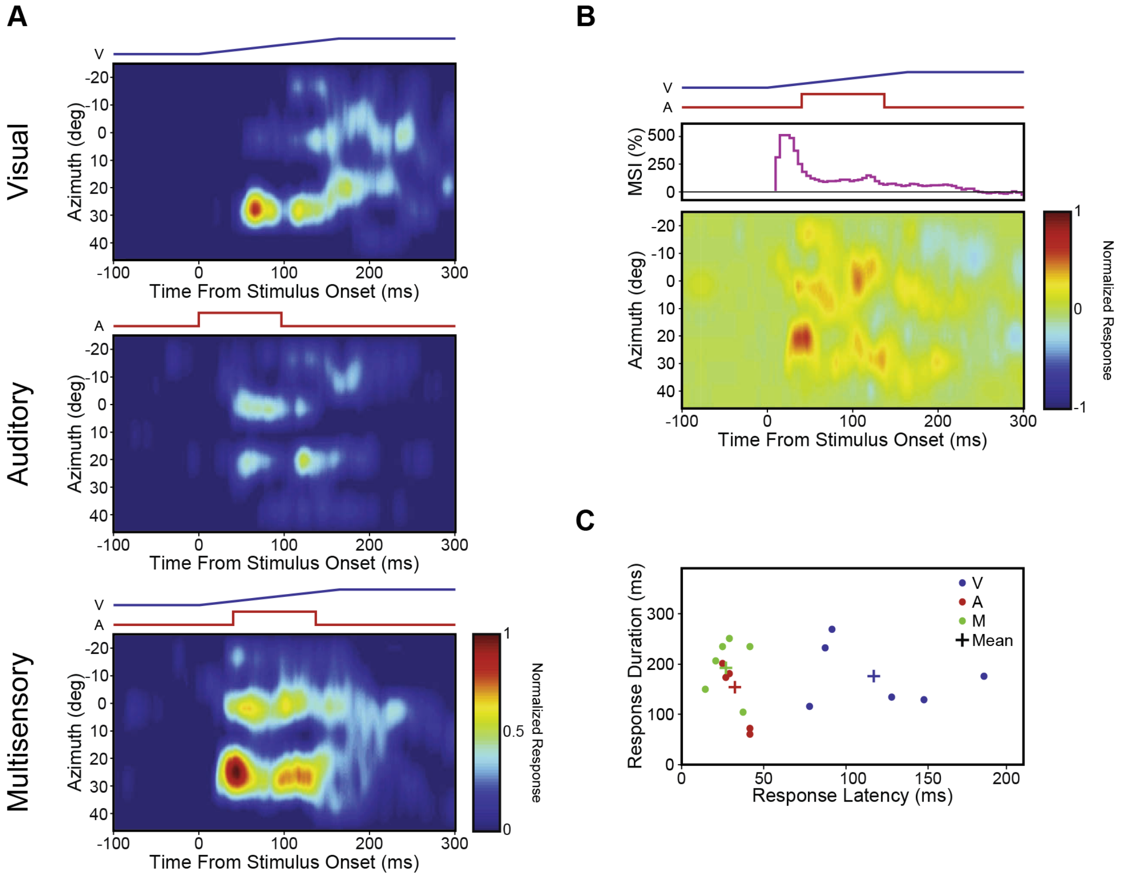
Figure 5-2: Representative example of an AES neuron exhibiting substantial changes of response and multisensory interaction as a function of changes in stimulus location. **A** – Visual, auditory, and multisensory SRFs plotted with each of the three representations being normalized to the greatest evoked response and the pseudocolor plots showing the relative activity scaled to this maxima. Symbols relate to the spatial locations of the stimulus pairings represented on the right (B). **B** – Rasters and spike density functions show the details of this neuron's responses to the visual stimulus alone (top row), auditory stimulus alone (middle row), and the combined visual–auditory stimulus (bottom row) presented at three different azimuthal locations (circle, square, and star on the receptive field plots in (A) show the stimulus locations; columns show the evoked responses at these three different locations). Note the pairing of effective visual and auditory stimuli resulted in no interaction (B, circle and square columns), pairings at a location in which the visual and auditory stimuli were less effective resulted in significant response enhancement (B, star column) (**P < 0.01).

Cortical multisensory SRFs reveal striking non-linear interactions

Perhaps the most interesting element of this SRF heterogeneity however, was the organization of the multisensory SRFs of these neurons, which almost never could be predicted on the basis of a simple linear addition of the component unisensory SRFs (Figure 5-2). Indeed, the multisensory SRF was found to be most typically comprised of zones of superadditive, additive and subadditive interactions. Analyses developed to probe the functional architecture of these different interactive regions found that the primary determinant of interactive mode (i.e., super-, sub- or additive) for a given multisensory pairing at a specific location was unisensory effectiveness. Pairings at weakly effective locations within the unisensory SRFs typically resulted in superadditive interactions. In contrast, pairings at the hot spots of the SRFs resulted in subadditive interactions, whereas pairings at locations of intermediate effectiveness most often gave rise to additive interactions. On the basis of these relationships, we have proposed a primacy of the in- verse effectiveness principle over the spatial principle, in that space appears to be important only by nature of how it impacts the efficacy of response.

Toward the creation of spatiotemporal receptive fields

In addition to these analyses that have focused on the spatial architecture of cortical multisensory neurons and the interactions that they exhibit, we have recently extended this framework to include the dimension of time. Prior work has revealed the importance of temporal factors in multisensory interactions, specifically by showing that the temporal relationship between the paired stimuli is a key determinant of the sign and magnitude of the resultant interaction (Royal et al., 2009). Extending these observations, we have posited that the temporal dynamics of the evoked sensory responses are likely to play an important role in multisensory integration. To test this idea, we have created a spatiotemporal receptive field plot, in which responses are plotted as a function of both spatial location (in one dimension – as opposed to the two-dimensional SRF plots) and time. Application of these methods to AES multisensory neurons has revealed a previously unappreciated spatiotemporal complexity to the receptive fields of these neurons (Figure 5-3). Once again, the critical observation in these spatiotemporal receptive field analyses is that the multisensory transform (i.e., superadditivity, subadditivity) is tightly linked to response efficacy. Thus, the individual unisensory responses are typically characterized by epochs of higher and lower response. Within epochs of weak response, the probability of superadditive interactions is greatly enhanced. In contrast, during periods of vigorous response, subadditive interactions are the typical response mode. Perhaps most revealing in these spatiotemporal receptive field analyses in AES neurons has been the unveiling of two important temporal epochs in the multisensory response – an early phase during which there is weak or no unisensory responses yet a defined multisensory response, and a late period after which the unisensory responses have ended and the multisensory response remains. Together, these temporal dynamics appear to form the basis for the speeding of responses and extended discharge durations that have been known to characterize multisensory responses (Royal et al., 2009).


A
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Visual
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300
Time From Stimulus Onset (ms)
A
Auditory
Azimuth (deg)
Time From Stimulus Onset (ms)
V
A
Multisensory
Azimuth (deg)
Time From Stimulus Onset (ms)
1
0.5
0
Normalized Response
B
V
A
MSI (%)
500
250
0
Azimuth (deg)
Time From Stimulus Onset (ms)
1
0
-1
Normalized Response
C
Response Duration (ms)
300
200
100
0
Response Latency (ms)
0
50
100
150
200
● V
● A
● M
+ Mean

Figure 5-3: Spatiotemporal receptive fields (STRFs) produced from a visual–auditory multisensory neuron recorded from cortical area AES. **A** – Visual (top), auditory (middle), and multisensory (bottom) STRFs aligned such that the relative timing of the stimuli depicted in the multisensory condition is preserved across panels. **B** – The difference STRF generated by subtracting the predictive multisensory STRF (linear sum of the visual and auditory STRFs) from the true multisensory STRF. Warmer colors reflect areas where the actual multisensory response exceeds the predicted multisensory response. The curve shown in the top panel represents the magnitude of multisensory integration (%) as the response evolves over time. **C** – Scatterplot highlights the relationship between response latency and response discharge duration plotted as a function of the stimulus condition. Plus signs represent the mean values for each stimulus condition. Note the leftward and upward shift in the multisensory response relative to the auditory and visual responses, reflecting the speeded and longer lasting responses, respectively.

A preliminary view into SRF architecture in SC neurons

We have recently extended our SRF approaches to the cat SC, where we have focused on defining the spatial architecture and integrative features of a small population of visual–auditory neurons in three animals. The recording and analysis methods for these experiments were identical to those conducted in AES (Carriere et al., 2008; Royal et al., 2009).

Multisensory SC neurons exhibit marked response differences within their spatial receptive fields

A total of 56 sensory responsive neurons were isolated from the intermediate and deep layers of the SC. Of these, 34 (61%) were multisensory neurons responsive to (or influenced by) visual and auditory stimuli. This was further subdivided into 13 neurons in which a systematic analysis of a sufficiently large number of locations (>12) within the classical excitatory receptive field were sampled, leading to the creation of a SRF for the visual, auditory and multisensory (i.e., combined visual–auditory) conditions (note that all SRF maps are created using a polar coordinate frame- work). Prior to this SRF analysis, a preliminary qualitative mapping of the visual and auditory receptive fields of these neurons revealed a high degree of spatial overlap, consistent with prior observations (Carriere et al., 2008). When examined using identical stimuli that only differed in their spatial location, the visual, auditory, and multisensory response profiles of each of the well-characterized neurons exhibited significant differences as a function of stimulus location. Figure 5-4 shows the SRF architecture of two representative SC neurons. In 11 of the 13 (85%) well-characterized neurons, this SRF heterogeneity was characterized by multiple (two or more) regions of elevated response surrounded by regions of significantly lesser response (i.e., multiple hot spots). For the majority (7/11) of these neurons, when the SRF architecture was compared between the visual, auditory and multisensory conditions, there was a general agreement in the topography of the spatial structure. Thus, a neuron with a single hot spot in the visual SRF at a specific location was likely to have a singular hot spot in the auditory and multisensory conditions at a similar location. However, several of the sampled neurons showed a significant spatial misregistry between these regions of maximal response. Nonetheless, and de- spite this general structural similarity across modalities, a comparison of the multisensory SRF with that predicted by a simple addition of the visual and auditory SRFs revealed a complexity to the combinatorial operations not captured by a simple summative model. In addition, a small preliminary sample of neurons has been tested to see how stable SRF architecture is over time (data not shown). These analyses reveal a good degree of constancy to SRF organization.

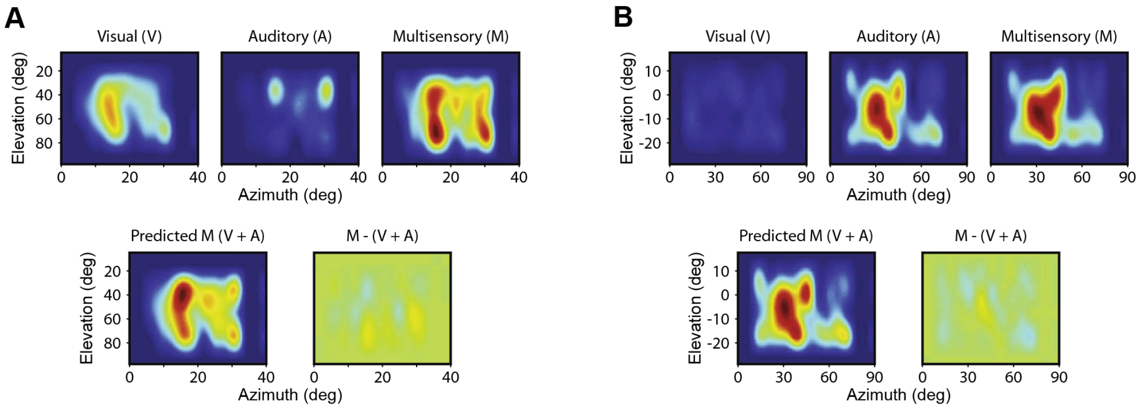

Figure 5-4: **A** – Representative example of the spatial receptive field (SRF) architecture of an individual multisensory superior colliculus neuron. Visual, auditory, and multisensory SRFs are shown at the top, along with the predicted SRF derived by simple addition of the visual and auditory SRFs (V + A) and a contrast plot showing the difference between the actual multisensory response and this predicted response (M - [V + A]). In the pseudocolor plots on the bottom panel, warmer colors represent superadditive interactions and cooler colors represent subadditive interactions. Note the difference in the actual multisensory response when compared with the additive prediction. **B** – A second example of the spatial receptive field (SRF) architecture of a multisensory superior colliculus neuron. Conventions are the same as in (A) Again, note the differences between the predicted and actual multisensory responses, which are best captured in the contrast plot (M - [V + A]). Note also in this example the near absence of an evoked visual response, but the clear modulation apparent in the multisensory profiles.

Influence of SRF architecture on multisensory interactions

As alluded to above, the multisensory responses of the individual SC neurons could not be readily predicted based on a simple addition of their unisensory response profiles. However, a more detailed analysis of these multisensory responses suggests that a given neuron's SRF organization may play an important role in determining the product of a multisensory interaction. When examined for their capacity to generate significant non- additive multisensory interactions (i.e., super- and subadditive changes) as a function of stimulus location, it was found that these interactions were produced only in discrete zones within the neuron's SRF(s). It is important to point out that in the current experimental design stimuli were always physically identical in all respects except for location (i.e., same intensity, contrast, frequency, etc.).

An example of this spatial complexity in the integrative architecture of SC neurons is shown in the example neuron depicted on the left half Figure 5- 4. In this neuron, substantial heterogeneity is seen in the spatial structure of the visual and auditory SRFs, and a third unique topography emerges under multisensory conditions. A contrast analysis between the predicted and actual multisensory responses reveals zones of significant superadditive interactions (warm colors) and zones of significant subadditive interactions (cool colors). Within these zones the actual multisensory response differed significantly from that predicted on the basis of an additive model. A second example neuron is shown on the right half of Figure 5-4. In contrast to the neuron illustrated on the left, this neuron appears to be unresponsive to visual stimuli (but has a robust auditory response). Nonetheless, the pairing of the auditory and visual stimuli results in a multisensory SRF profile that is different from the auditory SRF, illustrating a strong modulatory influence of the visual stimulus on the evoked auditory response. Although these two examples are qualitatively quite distinct, both appear to follow a similar combinatorial principle in which the gain (and sign) of the multisensory interaction appeared to be largely a function of stimulus efficacy at the tested locations. Thus, whereas pairings at locations in which robust visual and auditory responses are evoked results in either additive or subadditive interactions, pairings at weakly effective locations typically result in superadditive interactions. These two examples are representative of the population of SC multisensory neurons recorded, and highlight how multisensory interactions are critically dependent upon stimulus efficacy, which in turn is strongly dependent upon the unisensory receptive field architecture(s) of the studied neuron. Figure 5-5 illustrates these interrelationships in a much more concrete manner. Here, when we examine the response dynamics at two different locations within the unisensory and multisensory SRFs, we see that whereas the combination of weakly effective stimuli results in a superadditive multisensory response (left panel, red trace), the combination of highly effective stimuli results in subadditive interactions (right panel, red trace).

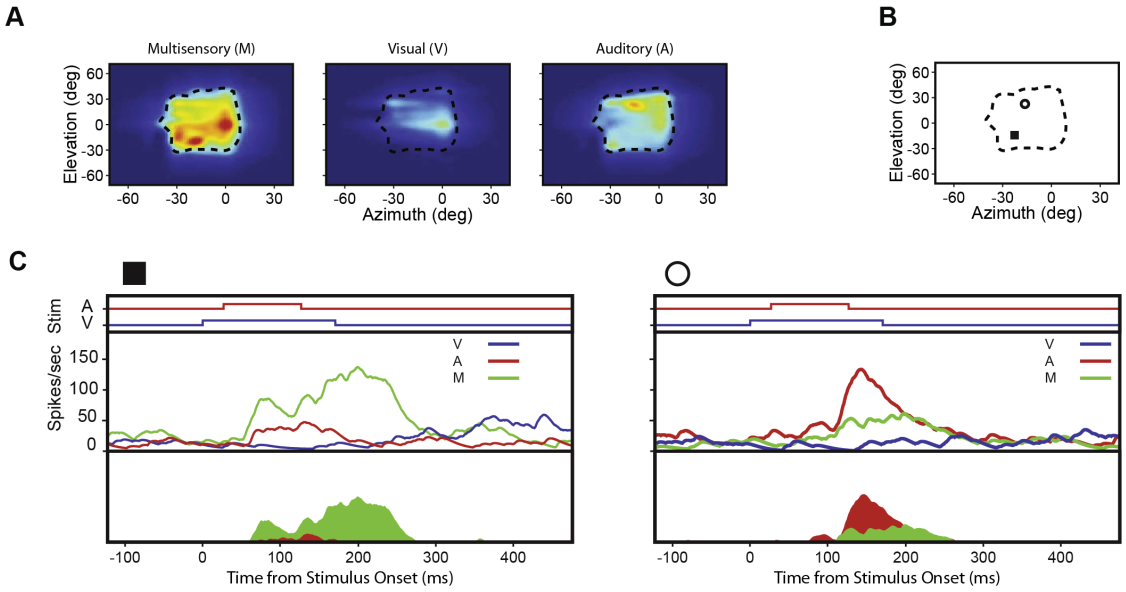

Figure 5-5: An example of a SRF analysis in an SC neuron illustrating the relationship between stimulus effectiveness and multisensory integration as a function of space. **A** – Spatial receptive fields (SRF) for this visual–auditory neuron. Warmer colors indicate higher evoked firing rates. The borders of the multisensory SRF are outlined with a dotted black line in all three panels. **B** – Stimulus locations for two spatially coincident multisensory pairings (circle and square) within the SRF. **C** – Evoked responses for these two locations for the visual, auditory and multisensory conditions. Note that whereas the pairing at a weakly effective location (square) results in a large superadditive multisensory interaction, the pairing at a location in which a vigorous auditory response could be evoked (circle) results in a clear subadditive interaction.

Population analyses reveal additional features of SRF architecture

An analysis of the small population of recorded visual–auditory neurons revealed several additional SRF and multisensory integrative characteristics. Depicted in Figure 5-6a is a polar plot analysis representing activity and integrative capacity as a function of spatial location for the population of sampled neurons. Although these plots suggest a reasonable degree of symmetry to the visual, auditory and multisensory SRFs of this population, several notable features emerge. First, activity is almost invariably greater under multisensory conditions, as represented by the greater response area shown in the multisensory polar plot. This finding is further reinforced by the data represented in Figure 5-6b, and which show that the vast majority of tested multisensory conditions resulted in response gains (i.e., enhancements). When the population means are compared across the unisensory and multisensory conditions, this response gain is strongly evident (Figure 5-6c). Thus, whereas the mean visual and auditory responses were 27 and 33 spikes/trial, respectively, the mean multisensory response was 45 spikes/trial, a significant enhancement ($p < 0.001$). A final intriguing observation that is most apparent in the polar plots is that multisensory gain is not uniformly or symmetrically distributed in space, but rather appears to be greatest along the horizontal meridian.

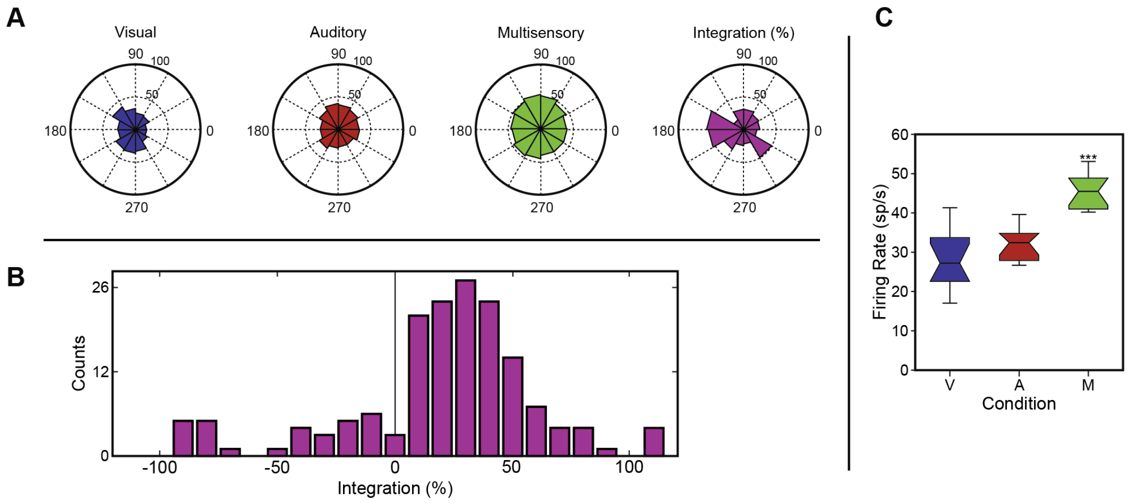

Figure 5-6: Population analysis for the well-characterized multisensory SC neurons. **A** – Polar plots depict the mean spatial response distributions for all three conditions as well as for the multisensory interaction. Note the fairly uniform distributions for each of the conditions, yet the clear bias along the horizontal meridian for the integration profile. **B** – Bar graph shows the magnitude and sign (i.e., >0 = enhancement; <0 = depression) for all tested multisensory interactions in this sample of SC neurons. Note that each neuron contributes multiple observations to this distribution because of the large number of sampled locations. **C**– Mean firing rate distributions across the different conditions. Note the significant gain under multisensory conditions.

A comparison of SRF organization in cortical and subcortical multisensory circuits

In the preliminary analysis of SC neurons conducted here, we demonstrate for the first time that the spatial receptive field architecture of multisensory neurons in the cat SC is heterogeneous and complex; a finding previously established for multisensory cortical neurons (Carriere et al., 2008). These findings add a dimension to our understanding of the spatial structure of the receptive fields of these neurons, which have been traditionally depicted as bordered regions within which a sensory response can be evoked (i.e., the excitatory receptive field). The finding of significant response differences within these border regions is in many respects not surprising given the large size of the receptive fields, and the fact that the underlying neural basis of these receptive fields (i.e., their dendritic extent and input architecture) is unlikely to be uniformly distributed. In fact, analysis of unisensory systems with large receptive fields has revealed that response heterogeneity is the rule rather than the exception (Fitzgerald et al., 2006; Hubel & Wiesel, 1962; Ozeki et al., 2004; Pena, 2003; Pollen et al., 2002).

Subtle differences are seen in the SRF organization of AES and SC multisensory neurons

A comparison of the different SRFs of the same SC neuron revealed there to be a global similarity in their structure, with the number of hot spots and the location of these zones being similarly distributed across modalities. Such commonalities may suggest that the overall structure of the SRF is dictated by fixed anatomical and/or biophysical constraints, such as the extent of the dendritic arbor. Intriguingly, these similarities are much less evident in cortical multisensory neurons (Carriere et al., 2008). This difference may be reflective of more heterogeneity in the inputs from the different modalities to this cortical domain, or may simply be derivative of the less spatiotopic order that is known to characterize AES cortex.

The functional utility of SRF heterogeneity

The utility of unisensory (i.e., visual, auditory) SRF heterogeneity as a functional construct remains in question. One plausible explanation has come from studies in the visual system that have shown the spatial (and spatiotemporal) structure in receptive fields can be an efficient means of encoding spatial dynamics as would be seen with moving stimuli (Fiset & Dore, 1996; Li et al., 2008; Victor et al., 1994). Future work will explore this issue for unisensory and multisensory SC neurons. From a multisensory perspective, SRF heterogeneity has clear functional consequences for the multisensory interactions manifested by these neurons. Most importantly, these interactions, which on first blush seem exceedingly complex, can be reduced to a relatively simple concept that is closely tied to SRF structure. Stimulus pairings at weakly effective locations within the SRF typically result in large and often superadditive response enhancements, whereas pairings at highly effective locations (i.e., hot spots) generally give rise to subadditive interactions. This finding is in good agreement with prior work in the SC (and other multisensory structures) that has detailed the principle of inverse effectiveness as a key feature characterizing multisensory interactions (Meredith & Stein, 1983, 1986b; Wallace et al., 1992). Although the functional value of such an organization remains unknown, one clear consequence of such a structure lies in its ability to amplify signals within weakly effective regions of the unisensory SRFs during multisensory conditions, effectively smoothing the spatial response profile of the neuron and ensuring more uniform and reliable activation to stimulation within the more globally defined receptive field. These preliminary results presented here represent one of the first efforts to provide a more accurate phenomenological description of receptive field architecture and its impact on multisensory interactions in the SC, with the ultimate goal of gaining a better view into the mechanistic processes that support multisensory processes. Although the current study focused only in the spatial dimension, ongoing studies are expanding these approaches to provide comprehensive descriptions of the spatiotemporal receptive field architecture of these neurons (Royal et al., 2009). Use of such a construct will shed important light on the dynamism inherent in multisensory circuits – a dynamism that is undoubtedly a result of the inherent stimulus complexities that characterize our sensory world.

Acknowledgements

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CHAPTER VI

STIMULUS INTENSITY MODULATES MULTISENSORY TEMPORAL PROCESSING

This paper is under review in the journal 'Neuropsychologia' as: Krueger Fister J, Stevenson RA, Nidiffer AR, Barnett ZP, and Wallace MT (2016). Stimulus intensity modulates multisensory temporal processing.

Abstract

One of the more challenging feats that multisensory systems must perform is to determine which sensory signals originate from the same external event, and thus should be integrated or "bound" into a singular perceptual object or event, and which signals should be segregated. Two important stimulus properties impacting this process are the timing and effectiveness of the paired stimuli. It has been well established that the more temporally aligned two stimuli are, the greater the degree to which they influence one another's processing. In addition, the less effective the individual unisensory stimuli are in eliciting a response, the greater the benefit when they are combined. However, the interaction between stimulus timing and stimulus effectiveness in driving multisensory-mediated behaviors has never been explored – which was the purpose of the current study. Participants were presented with either high- or low-intensity audiovisual stimuli in which stimulus onset asynchronies (SOAs) were parametrically varied, and were asked to report on the perceived synchrony/asynchrony of the paired stimuli. Our results revealed an interaction between the temporal relationship (SOA) and intensity of the stimuli. Specifically, individuals' were more tolerant of larger temporal offsets (i.e., more likely to call them synchronous) when the paired stimuli were less effective. This interaction was also seen in response time (RT) distributions. Behavioral gains in RTs were seen with synchronous relative to asynchronous presentations, but this effect was more pronounced with high-intensity stimuli. These data suggest that stimulus effectiveness plays an underappreciated role in the perception of the timing of multisensory events, and reinforces the interdependency of the principles of multisensory integration in determining behavior and shaping perception.

Introduction

Our daily environment is filled with an abundance of information that our different sensory systems utilize in order to allow us to successfully navigate the world. Despite the fact that many of the objects and events in our world are specified by information carried by multiple senses, we perceive these as singular and unified. In order to create such a unified percept, the brain must be able to "bind" information that belongs together and segregate information that should be separate. The binding process by which multisensory cues are actively synthesized – a process that represents a component of multisensory integration - has been the subject of much study. Collectively, this work has revealed dramatic changes associated with combining information across multiple senses; changes that frequently result in substantial benefits to behavior (Amlot et al., 2003; Frassinetti et al., 2002; Lovelace et al., 2003) and striking alterations in perception (McGurk & MacDonald, 1976; *The neural bases of multisensory processes*, 2012; Shams et al., 2002).

To solve this “binding problem,” sensory systems rely upon the statistical properties of the different sensory signals, two of the most important of which are space and time. Multisensory (e.g., visual-auditory) stimuli that are spatially and temporally concordant tend to influence one another’s processing, and may ultimately be integrated or bound, whereas those that are discordant in space and/or time tend to not influence the processing of one another (Conrey & Pisoni, 2006; Hairston, Burdette, Flowers, & Wallace, 2005; Keetels & Vroomen, 2005; Macaluso et al., 2004; Powers et al., 2009; Stevenson, Zemtsov, et al., 2012; Stevenson, Fister, et al., 2012; van Atteveldt et al., 2007; van Wassenhove et al., 2007; Vroomen & de Gelder, 2004; Vroomen & Keetels, 2010; Wallace & Stevenson, 2014). Furthermore, it has also been shown that stimuli that are weakly effective on their own tend to give rise to the largest gains when combined (James & Stevenson, 2012; James et al., 2009; James et al., 2012; Ross, Saint-Amour, Leavitt, Javitt, et al., 2007; Senkowski et al., 2011; Stein et al., 2009; Stevenson & James, 2009; Stevenson, Bushmakin, et al., 2012). Collectively, these integrative principles make a great deal of ethological sense, in that spatial and temporal proximity typically signal a common source, and in that it is highly adaptive to accentuate multisensory gain when each of the sensory signals is weak or ambiguous when presented alone.

Recently, a number of studies have focused on how temporal factors influence the nature of human multisensory perceptual judgments (Billock & Tsou, 2014; Conrey & Pisoni, 2006; Grant et al., 2004; Macaluso et al., 2004; van Wassenhove et al., 2007; Vroomen & de Gelder, 2004; Vroomen & Keetels, 2010). One useful construct associated with this work is the concept of a multisensory temporal binding window, defined as the epoch of time within which multisensory stimuli can influence one another’s processing. The window within which multisensory influences can be demonstrated appears to be surprisingly broad, spanning several hundred milliseconds

(Hillock et al., 2011; Hillock-Dunn & Wallace, 2012; Powers et al., 2009; Powers et al., 2012; Sarko et al., 2012; Stevenson et al., 2013). In addition, these studies and others have revealed a number of other salient characteristics concerning multisensory temporal acuity. These include that it: 1) has a great deal of individual variability (Stevenson, Zemtsov, et al., 2012; van Eijk et al., 2008), 2) differs depending upon stimulus type and task (Kasper et al., 2014; Megevand et al., 2013; Stevenson & Wallace, 2013; van Eijk et al., 2008, 2010; Vroomen & Stekelenburg, 2011), and 3) is malleable in response to perceptual training (Keetels & Vroomen, 2008; Powers et al., 2009; Powers et al., 2012; Schlesinger et al., 2014; Stevenson et al., 2013; Stevenson, Fister, et al., 2012; Vroomen et al., 2004) and across development (Hillock et al., 2011; Hillock-Dunn & Wallace, 2012; Joanne Jao et al., 2014; Johannsen & Roder, 2014; Lewkowicz, 2012; Polley et al., 2008; Shi & Muller, 2013) and aging (Bates & Wolbers, 2014; DeLoss et al., 2013; Diaconescu et al., 2013; Freiherr et al., 2013; Hugenschmidt et al., 2009; Mahoney et al., 2014; Mahoney et al., 2012; Mozolic et al., 2012; Stevenson et al., 2015).

Although these studies have illustrated the central importance of time in dictating human multisensory interactions, other studies have focused on the roles of space (Bertelson & Radeau, 1981; Ghose & Wallace, 2014; Kadunce et al., 2001; Krueger et al., 2009; Macaluso et al., 2004; Mahoney et al., 2015; Meredith & Stein, 1986b, 1996; Radeau & Bertelson, 1974; Royal et al., 2009; Royal et al., 2010; Sarko et al., 2012; Vroomen et al., 2001; Wallace et al., 2004) and effectiveness (James et al., 2012; Kim & James, 2010; Kim et al., 2012; Leone & McCourt, 2013; Liu et al., 2013; Nath & Beauchamp, 2011; Stevenson & James, 2009; Werner & Noppeney, 2010; Yalachkov et al., 2015). Collectively, we have learned a great deal from these studies about how stimulus-related factors shape the multisensory process, but most have treated time, space and effectiveness as independent contributors to the final multisensory product. In fact, these stimulus factors are complexly intertwined, with manipulations in one having effects upon the other. For example, simply changing the spatial location of an identical stimulus will impact the effectiveness of that stimulus given the differences in spatial acuity for different regions of space (Nidiffer et al., 2015 (in revision); Stein et al., 1989). Reinforcing the importance of examining these interactions in more detail, recent neurophysiological studies in animal models have shown that manipulating one aspect of a multisensory stimulus (e.g., spatial location) has consequent effects in both the temporal and effectiveness dimensions (Carriere et al., 2008; Ghose & Wallace, 2014; Krueger et al., 2009; Royal et al., 2009). Indeed, this work has suggested that stimulus effectiveness may play a more preeminent role than space and time in dictating multisensory interactions at the neural level. Extending this work into the domain of human performance, recent studies have shown a strong interdependency between time and space (Keetels & Vroomen, 2005; Krueger et al., 2009; Stevenson, Fister, et al., 2012). For example, Keetels and Vroomen (2005) showed that judgments concerning the order of auditory and visual stimuli were more precise when they were presented in disparate spatial locations. Stevenson and colleagues (2012) showed that individuals were more likely to perceive auditory and visual stimuli as synchronous when they were presented at peripheral relative to foveal locations.

The present study seeks to expand upon these previous findings by examining for the first time the interaction between the temporal relationship of paired audiovisual stimuli and their relative effectiveness. Specifically, we tested the impact that manipulations of stimulus effectiveness (accomplished via changes in stimulus intensity) have on the ability of an individual to report audiovisual stimulus asynchrony. Our results illustrate that the relative effectiveness of the paired stimuli do in fact modulate how they are perceived in time. Furthermore, these studies revealed complex interactions between time and effectiveness in dictating the final behavioral outcome.

Methods

Participants

Participants included 51 Vanderbilt undergraduate students (21 male, mean age =18.9, STD =1, age range =18-21) who were compensated with class credit. All recruitment and experimental procedures were approved by the Vanderbilt University Institutional Review Board (IRB). Data from participants who did not accurately report the perception of synchrony even when the auditory and visual presentation was objectively simultaneous (0ms stimulus onset asynchrony; SOA) at least 50% of the time were excluded from further analysis (N = 5). Data from one additional subject were excluded for responding synchronous for all trials irrespective of SOA resulting in 45 subjects being included in all data analysis. The present study is part of a larger study investigating the interrelationship of stimulus effectiveness, and stimulus spatial and temporal factors (Nidiffer et al., 2015 (in revision); Stevenson, Fister, et al., 2012).

Stimuli

Visual and auditory stimuli were presented using E-Prime version 2.0.8.79 (Psychology Software Tools, Inc; PST). Visual stimuli were presented on a Samsung Sync Master 2233RZ 120 Hz monitor arranged so that subjects were seated at a distance of 46 cm. All visual stimuli were white circles measuring 7 mm in diameter, or approximately 1° of visual angle. Visual stimuli were presented at 0° azimuth (in front of the subject) slightly above a fixation cross. Visual stimuli were presented at two luminance levels, 7.1 cd/m^2 (low) and 215 cd/m^2 (high) on a black background of 0.28 cd/m^2. Luminance values were verified with a Minolta Chroma Meter CS-100. Visual stimulus durations were 10 ms, with timing confirmed using a Hameg 507 oscilloscope with a photovoltaic cell.

Auditory stimuli were presented via a speaker mounted on the top of the monitor at 0° azimuth angled toward the participant. Speakers were mounted 2 cm, or 2.5° above their respective visual presentation. Auditory stimuli consisted of a frozen white-noise burst generated at 44100 Hz with the Matlab *rand* function with a 5 ms rise and 5ms fall cosine gate (Figure 6-1b). Auditory stimulus duration was held constant at 10 ms, with timing confirmed using a Hameg 507 oscilloscope. Auditory stimuli were presented at two intensity levels, 46 dB SPL (low) and 64 dB SPL (high), with a background noise at 41 dB SPL. All sound levels were verified with a Larson Davis sound-level meter, Model 814.

Audiovisual (AV) conditions consisted of pairs of the auditory and visual stimuli described above. Presentations were always spatially coincident at 0° azimuth and intensity levels were always matched (high-high and low-low). The temporal offset of the auditory and visual stimulus pairs were parametrically varied, including stimulus onset asynchronies (SOAs) of 0, 50, 100, and 200 milliseconds, with timing confirmed using a Hameg 507 oscilloscope. In all asynchronous cases, visual onset preceded auditory onset.

Procedure

Participants were seated inside an unlit WhisperRoom™ (SE 2000 Series) with their forehead placed against a Headspot (University of Houston Optometry) forehead rest locked in place. A chinrest and the chair height could be adjusted to the forehead rest to ensure a comfortable seating position. Participants were asked to fixate a cross located at 0° elevation and 0° azimuth at all times and were monitored by close circuit infrared cameras throughout the experiment to ensure compliance (for experimental setup, see Figure 6-1a and 6-1b).

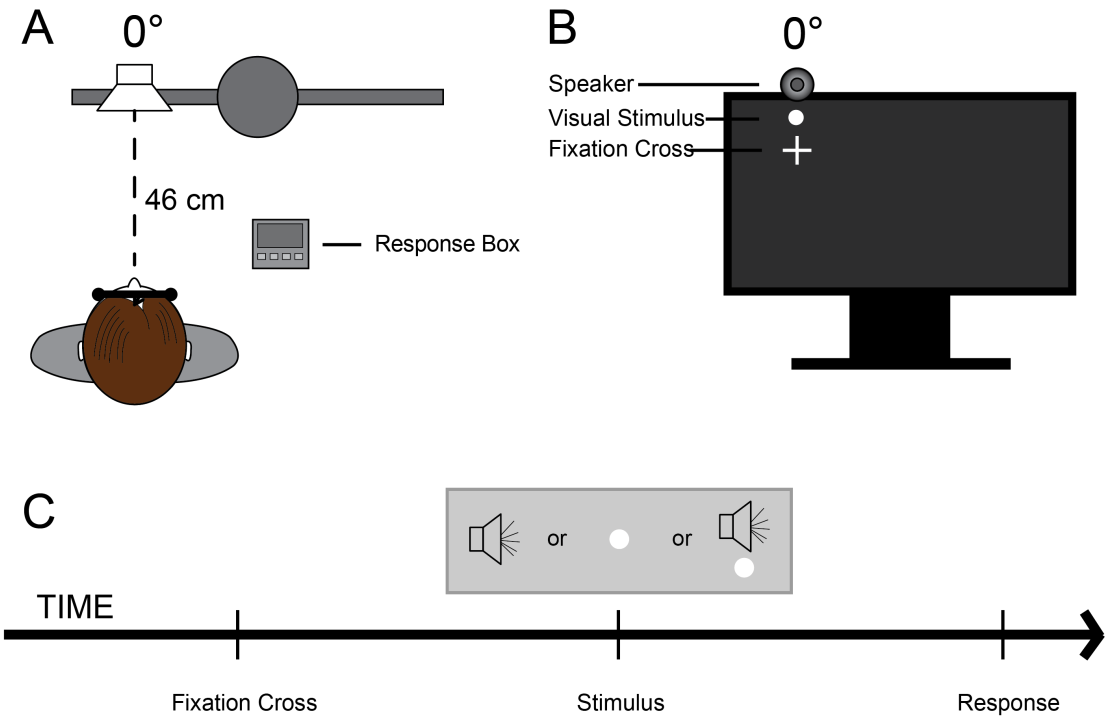

Figure 6-1: **A** – Participant set up indicating the participant’s location in relationship to the apparatus. **B** – Location of auditory and visual stimulus relative to fixation. **C** – Timeline of stimulus presentations.

The experiment began with detailed instructions, informing the participants that they would be presented with audiovisual stimuli, and that their task was to judge whether or not the stimuli were synchronous and to respond as quickly and accurately as possible. In the case that the participants did not perceive either the auditory or visual stimulus, they were instructed to report a unisensory perception. Participants were instructed to respond via a five-button PST serial response box were 1 = synchronous, 2 = asynchronous, 3 = visual only, 4 = audio only, and 5 = no stimulus detected. Understanding of the instructions was then confirmed, and the participants were given the opportunity to clarify any questions they had about the instructions. Participants were instructed to respond as quickly and as accurately as possible.

Each trial began with a fixation screen of 1 s displaying the fixation cross in the center of the visual field. After that time period the fixation cross disappeared and was followed by a blank screen with a duration jittered between 500 and 1000 ms, followed by the stimulus presentation. 250ms – 284ms after stimulus presentation, subjects were presented with the response prompt, “Was it synchronous?” Following the participant’s response and a 500ms delay, the fixation cross re-appeared, and the subsequent trial began. For a visual depiction of a trial, see Figure 6-1c. Twenty trials of each of the stimulus conditions (4 SOAs x 2 intensity levels, unisensory V x 2 intensity levels, unisensory A x 2 intensity level) were presented for a total of 240 trials.

Analysis

For each trial in which the participant perceived an audiovisual stimulus, both the response and the response time (RT) were recorded. RTs less than 250ms were discarded. Our primary analysis focused on rates of perceived synchrony. With each condition, rates of perceived synchrony were calculated as the proportion of trials in which the participant reported a synchronous percept out of all trials in that condition, in which they perceived both stimuli, or:

$$\frac{\#\ trials\ perceived\ synchronous}{\#\ trials\ perceived\ synchronus\ +\ \#\ trials\ perceived\ asynchronous}.$$

It should be noted that this explicitly excludes trials in which the participant did not perceive both unisensory components of the stimuli. Rates of perceived synchrony were compared across intensity levels and SOA.

A follow-up, exploratory analysis was conducted on RTs. First, mean RTs were calculated across trials of each condition for each individual. Mean RTs were compared across intensity levels and SOA. A second exploratory RT analysis was performed using a more rigorous cumulative distribution function (CDFs) analysis. CDFs were calculated and compared for correct trials of each condition, again averaging within each participant, and then across participants. Interactions between SOA and stimulus intensity in their CDFs were then assessed using a difference of difference calculation:

$$\left(CDF_{o\ ms\ high} - CDF_{(200\ ms\ high)}\right) - \left(CDF_{(0\ ms\ low)} - CDF_{(200\ ms\ low)}\right).$$

Results

Intensity effects on unisensory performance

To ensure that changes in stimulus intensity were actually manipulating stimulus saliency, a two-way, repeated-measures ANOVA (intensity x modality) confirmed that high intensity presentations were more effective than low intensity stimulus presentations ($F_{(1,39)} = 8.26$, $p = 0.0065$). Paired sample t-tests also revealed that accuracies decreased for both modalities from the high-saliency to the low-saliency condition (visual, high = 97.17%, low = 91.67%, t = 0.965, p = 0.045, d = 0.014 and auditory, high 97.08%, low = 93.75% t = 0.96, p = 0.051, d = 0.307).

Effects of stimulus effectiveness and temporal factors on judgments of audiovisual synchrony

Rates of perceived synchrony were measured for high- and low-intensity audiovisual stimuli presented at temporal offsets ranging from 0 ms (synchronous) to 200 ms (visual leading asynchronies). A two-way, repeated-measures ANOVA (intensity x SOA) was performed. A significant main effect was found for SOA ($F_{(3,44)} = 22.411$, $p = 8.03\times10^{-9}$, partial-$\eta^2 = 0.559$). As expected, rates of perceived synchrony decreased with increasing SOA (Figure 6-2a and 6-2b). The main effect for intensity was marginally significant ($F_{(1,44)} = 3.171$, $p = 0.082$, partial-$\eta^2 = 0.067$). Importantly, a significant interaction effect between SOA and intensity was also observed ($F_{(3,44)} = 13.219$, $p = 3.24\times10^{-6}$, partial-$\eta^2 = 0.270$).

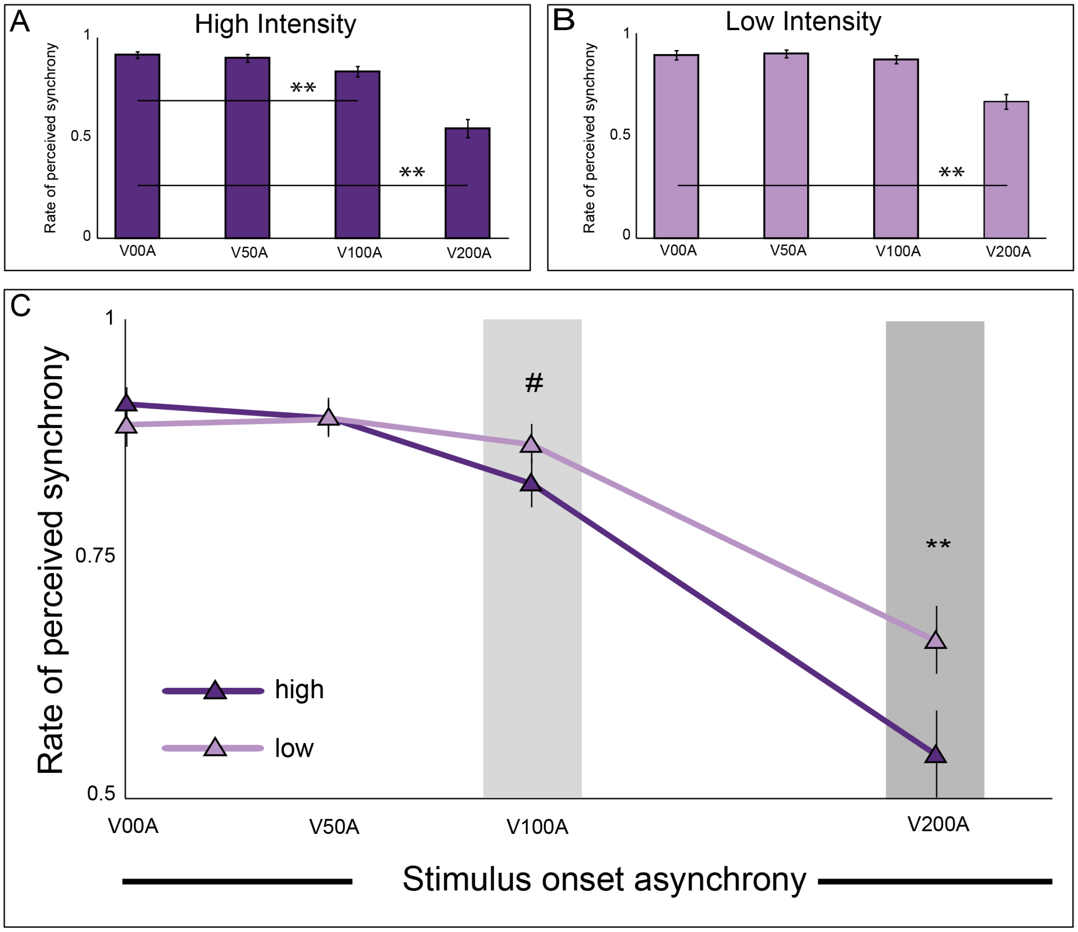

Figure 6-2: **A** and **B** – Bar graphs present the changes across SOA within each level of stimulus intensity. For both saliencies, perceived synchrony decreases with increasing SOA with faster changes occurring in the high-saliency condition. **C** – Line graphs present the changes in perception of synchrony across stimulus intensity levels. Most notably, subjects perceived audiovisual stimuli more often as synchronous for the largest SOA at the low saliency condition. For all panels, ** indicates $p < 0.0001$ # indicates p approaches 0.05.

To explore the interaction between SOA and intensity on these synchrony judgments, two sets of protected, follow-up, paired-samples *t*-tests were performed. First, t-tests were run comparing rates of perceived synchrony across SOAs (See Table 6-1 for detailed statistics). Rates of perceived synchrony were significantly reduced relative to synchronous presentations at the 100 and 200 ms SOA for the high-intensity stimuli, but only at the 200 ms SOA for the low intensity stimuli (Figure 6-2a and 6-2b). Second, paired t-tests were run across intensity levels at each SOA. A significant difference between rates of perceived synchrony between high and low intensity stimuli was observed only for the 200 ms SOA ($t = 3.5507$, $p = 8.48 \times 10^{-4}$, $d = 1.071$), where participants were more likely to report low intensity stimuli as synchronous relative to high intensity stimuli. No other SOAs showed significant differences between the two intensities (Figure 6-2c). Thus, the interaction showed that individuals were more likely to report asynchronous presentations as synchronous at lower levels of stimulus intensity.

Effects of stimulus intensity and temporal factors on response times

In addition to our analysis of the synchrony judgments of participants, mean RTs were also determined by averaging across subjects by SOA and intensity level (Table 6-2). Repeated measures ANOVA showed a main effect of SOA ($F_{(3,43)} = 2.630$, $p = 0.049$, partial-$\eta^2 = 0.039$). In contrast, no significant differences in mean RTs across intensities ($F_{(1,43)} = 1.260$, $p = 0.268$, partial-$\eta^2 = 0.028$) and no interaction effect between intensity and SOA ($F_{(3,43)} = 0.686$, $p = 0.566$, partial-$\eta^2 = 0.019$) were found.

Table 6-1. Rates of perceived synchrony relative to synchronous presentations

	High intensity		Low intensity	
SOA (ms)	*t*-score	*p*-value	*t*-score	*p*-value
50	1.39	n.s.	0.56	n.s.
100	4.05	$1.93e^{-4}$	1.10	n.s.
200	7.60	$5.61e^{-7}$	5.74	$5.61e^{-7}$

SOA – stimulus onset asynchrony

Table 6-2. Mean response times in ms

	High intensity		Low intensity	
SOA (ms)	Mean	St. Err.	Mean	St. Err.
0	421.5	29.7	429.1	27.9
50	420.1	26.1	401.6	26.0
100	433.2	29.6	434.5	25.8
200	457.6	28.0	427.8	23.9

SOA – stimulus onset asynchrony

St.Err – standard error

In addition to an analysis of mean RTs, a cumulative distribution function (CDF) analysis was also performed. CDFs were calculated for each subject and then averaged across participants for each condition. To explore the impact of time on these CDFs, differences between the CDFs at 0 ms SOA and 200 ms SOA for each individual were computed for both intensity levels (difference curves plotted in Figure 6-3a and 6-3b) and binned into 100 ms intervals for comparison. In the high intensity condition, there was a significant effect of SOA in the RT bins spanning from 200-1000 ms, where the 0 ms SOA was associated with significantly faster RTs than the 200 ms SOA. A similar pattern was seen in the low-intensity conditions, where RTs in the bins between 200-400 and 500-600 ms showed marginally faster RTs at the 0 ms SOA. Regardless of intensity level, the greatest difference invariably occurred during the early portion of the response distribution, as seen in Figure 6-3c. Here the difference in these response distributions were segmented into 100 ms bins for comparison, revealing an interaction effect where SOA showed a stronger impact on RT when stimuli were presented at high intensity levels relative to low intensity levels. Finally, to assess this interaction overall, an area-under-the-curve measure was taken for each individual's differences in response distributions across SOAs (Figure 6-3d). A direct comparison of these areas under the curve confirmed the results of the binned analysis, showing that SOA had a greater impact on stimuli presented at a high intensity level ($t = 28.32$, $p = 1.29e^{-14}$, $d = 8.539$).

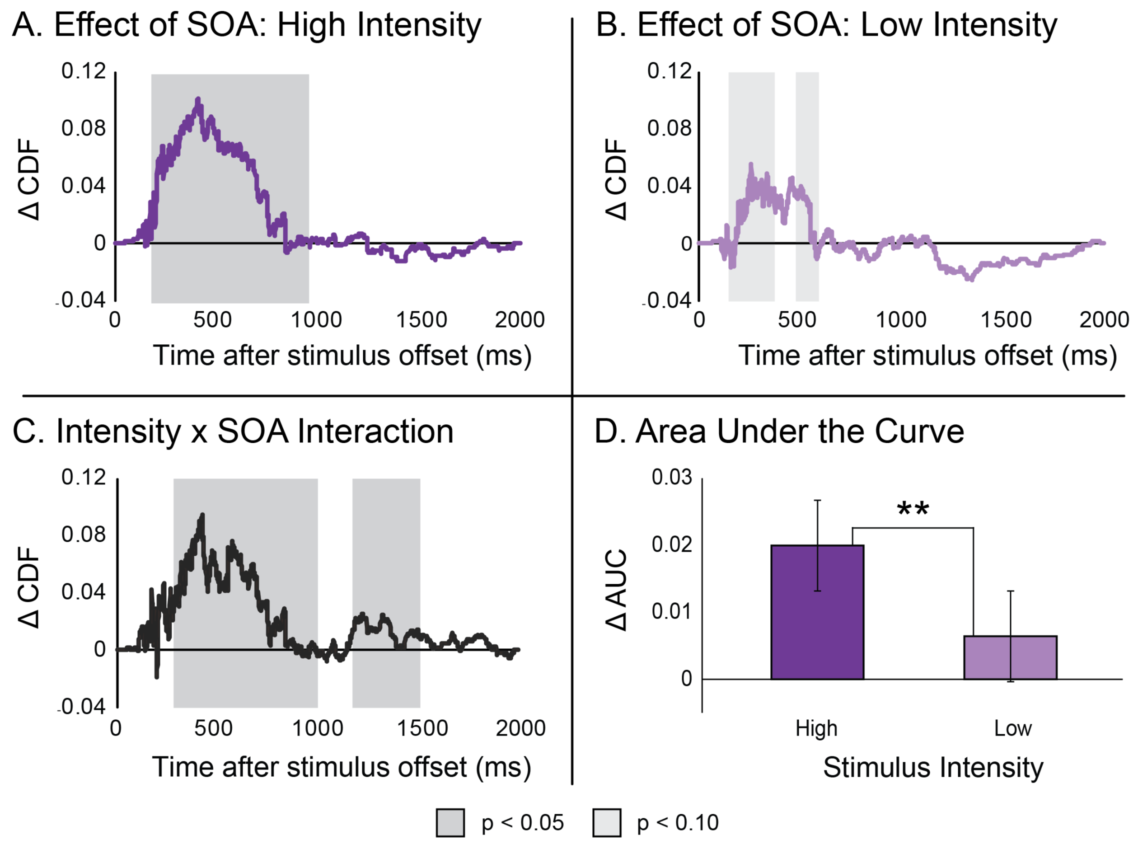

Figure 6-3: **A** and **B** – Differences in cumulative distribution functions measured with synchronous (0 ms SOA) and asynchronous (200 ms SOA) presentations with both high-intensity (Panel A) and low-intensity (Panel B) presentations. **C** – An interaction between SOA and stimulus intensity was observed using a difference-of-difference measure. The effect of SOA was significantly more pronounced with high- than with low-intensity stimuli. **D** – Area-under-the-curve measures were extracted from the CDF differences displayed in Panels A and B, providing a secondary measure of interactions between SOA and stimulus intensity. ** denotes a significant difference at an α-level of 0.05.

Discussion

Previous studies have established that manipulating space, time, and stimulus intensity can greatly alter multisensory integration and the associated neural, behavioral and perceptual responses. The present study extends this work by examining how stimulus timing and intensity interact to impact perceptual performance, showing a strong interdependency between timing and intensity in judgments of the synchrony/asynchrony of the paired stimuli (i.e., synchrony). Specifically, participants were significantly more likely to report asynchronous audiovisual stimuli as synchronous when stimulus intensity levels were lower. This novel finding illustrates that stimulus intensity plays an important and previously unreported role in the perception of the timing of multisensory events.

The results suggest that processing of multisensory stimuli that are weakly effective is less temporally precise than for more effective stimuli. Multisensory systems thus appear to compensate for increasing levels of stimulus ambiguity by increasing their tolerance for asynchronies, resulting in perceptual binding over a greater degree of temporal disparity. Adjusting the width of the temporal binding window would compensate in a manner that effects the overall magnitude of multisensory integration, a notion supported by the time-window-of-integration model (Colonius & Diederich, 2004). Ecologically, this result makes a good deal of sense, since in natural environments sensory inputs arriving from a proximal source are likely to be more intense and will arrive at their respective sensory organs in a more temporally congruent manner. In contrast, sensory information from an identical event that occurs at a greater distance from the individual will be of lower intensity and the temporal disparity at the point of the respective sensory organs will be increased. Thus, a greater tolerance for temporal offsets with low-intensity sensory signals is necessary in order to properly reflect the natural statistics of the environment. Furthermore, the nervous system may also expand its temporal filter for less effective stimuli in order to compensate for the necessity to acquire more information toward a behavioral judgment, These results parallel previous work showing that more peripherally presented audiovisual stimuli are more likely to be perceptually bound at wider temporal offsets (Nidiffer et al., 2015 (in revision); Stevenson, Fister, et al., 2012).

One hallmark feature in processing information from external and internal events is the brain's capability to continuously recalibrate and update ongoing neural processes in a dynamic fashion. This occurs particularly frequently when signals are noisy or less reliable as could be the case with low-intensity stimuli. Indeed, previous research has shown that the manner in which the nervous system integrates sensory information is adaptable according to the reliability of information in each sensory modality (Andersen et al., 2004; Beauchamp et al., 2010; Beierholm et al., 2009; Besson et al., 2010; Charbonneau et al., 2013; Clemens et al., 2011; Deneve & Pouget, 2004; Ernst & Banks, 2002; Fetsch et al., 2010; Fetsch et al., 2009; Fetsch et al., 2012; Helbig et al., 2012; Ma & Pouget, 2008; Nath & Beauchamp, 2011; Noppeney et al., 2010; Rohe & Noppeney, 2015).

Furthermore, multisensory systems are characterized by a great deal of plastic capacity, a feature that has been explored extensively in the temporal realm. Thus, through recalibration (Fujisaki et al., 2004; Vroomen et al., 2004) and perceptual learning (Powers et al., 2009; Powers et al., 2012; Schlesinger et al., 2014; Stevenson et al., 2013), it has been demonstrated that an individual's perception of synchrony and the window of time within which that individual will perceptually bind paired stimuli can be modified. Given the malleability of multisensory processing, it seems plausible then that these processes may become more liberal in the window of time with which they perceptually bind incoming sensory information based upon its reliability or intensity. Indeed, such real time recalibration of sensory integration has been reported previously in reference to stimulus reliability as determined by signal-to-noise ratio (Nath & Beauchamp, 2011). In this study, re-weighting of stimulus inputs based on reliability impacted the magnitude of multisensory integration in STS as demonstrated through fMRI. While the current data set cannot directly assess this hypothesis, this possible explanation is intriguing and warrants direct testing in future research.

Consistent with the results of the current study, one line of previous research has provided evidence that another aspect of multisensory temporal processing, the point of subjective simultaneity (PSS), can also be modulated by stimulus intensity. The PSS, which describes the temporal offset at which the perception of synchrony is maximal, is generally found when the visual component of a multisensory stimulus slightly precedes the auditory component. Studies investigating the role that stimulus intensity has on the PSS have generally shown that with decreases in stimulus intensity, the PSS shifts to an SOA with a greater auditory lag (Boenke et al., 2009; Neumann et al., 1992). Furthermore, stimuli presented in the periphery have also been shown to have a PSS associated with a greater visual-first SOA (Arden & Weale, 1954; Zampini et al., 2003), a result that may be derivative of changes in stimulus effectiveness. Furthermore, prior work from our lab has shown that the window within which an individual perceives temporal synchrony is in fact broader in the periphery (Stevenson, Fister, et al., 2012). This extension beyond measures of the PSS is vital, as manipulations of other stimulus factors, such as spatial disparity, have been shown to impact the window of integration without impacting the PSS (Keetels & Vroomen, 2005). The current study, however, provides the first evidence that direct manipulations of stimulus intensity alter the temporal tolerance for perceived simultaneity.

In accord with the changes in rates of perceived synchrony across levels of stimulus intensity, exploratory analysis of changes in response time CDFs across SOAs and intensity levels were also observed. Individuals were slower to respond to stimuli presented at longer SOAs, but this effect was smaller with low-intensity stimuli. This interaction effect in RTs provides converging evidence with the simultaneity judgment data, and reinforces the conclusion that at lower intensity levels (i.e., weaker effectiveness) multisensory systems are more tolerant of temporal offsets and thus capable of binding audiovisual stimuli over larger temporal intervals.

The role of effectiveness and timing is also important in the study of atypical sensory and multisensory perception. Specifically, effectiveness and timing play a role in dysfunctional multisensory integration in a number of clinical populations. For example, the ability to benefit from seeing an speaker’s face while conversing in a noisy environment is dependent upon the effectiveness of the auditory signal, but individuals with schizophrenia (Ross, Saint-Amour, Leavitt, Molholm, et al., 2007) and autism (Brandwein et al., 2013) show deficits in the amount of perceptual benefit they gain at low levels of stimulus effectiveness. Furthermore, dysfunction in temporal processing of multisensory stimuli have also been shown in individuals with autism (Baum et al., 2015; Bebko et al., 2006; de Boer-Schellekens et al., 2013; Foss-Feig et al., 2010; Kwakye et al., 2011; Stevenson, Segers, et al., 2014; Stevenson, Siemann, Woynaroski, et al., 2014a; Stevenson, Siemann, Schneider, et al., 2014; Stevenson, Siemann, Woynaroski, et al., 2014b; Wallace & Stevenson, 2014; Woynaroski et al., 2013), schizophrenia (Martin et al., 2013), and dyslexia (Froyen et al., 2011; Hairston, Burdette, Flowers, Wood, et al., 2005; Virsu et al., 2003). Since having an appropriately sized temporal binding window ensures proper multisensory integration, one avenue of future research should investigate whether or not clinical populations with enlarged temporal windows will show a corresponding widening of these windows with changing stimulus properties (i.e., stimulus intensities as described in the current study) or with increasing levels of stimulus complexity (Stevenson & Wallace, 2013; Vroomen & Stekelenburg, 2011). Furthermore, given previous demonstrations of how one can improve multisensory temporal precision through perceptual learning (Powers et al., 2009; Powers et al., 2012; Schlesinger et al., 2014; Stevenson et al., 2013), future studies applying such training to clinical populations as possible therapeutic tool may prove fruitful. Emerging evidence suggests enormous developmental plasticity in multisensory temporal function (Hillock et al., 2011; Hillock-Dunn & Wallace, 2012; Stevenson et al., 2013). Such developmental malleability could potentially be directed in clinical populations to ameliorate some of the changes in sensory function. Indeed, audiovisual training in children with reading disabilities has been used as a tool to improve reading comprehension (Kujala et al., 2001; Veuillet et al., 2007). Thus, delineating the temporal factors and constraints for multisensory binding and integration in normative populations builds the foundation for comparisons in clinical populations, which may provide key insights into the design of effective interventional measures.

Conclusions

The study presented here provides novel evidence of a relationship between the perception of multisensory stimuli in relation to their stimulus effectiveness and their temporal synchrony. Specifically, these data suggest that the effectiveness of a stimulus presentation impacts how the temporal dynamics of the stimulus presentation are perceived, where tolerance for stimulus asynchronies is increased as stimulus effectiveness decreases. While the present study clearly indicates stimulus-intensity dependent changes in the window of temporal integration, it is limited to only two saliency levels, suggesting further exploration of this effect with a broader range of SOAs and salience levels that span the dynamic range of behavioral responses to provide a full picture of how the temporal principle and inverse effectiveness interact.

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CHAPTER VII

GENERAL DISCUSSION

The central theme of the current thesis is the exploration of mechanisms within which multisensory stimuli are processed across various brain structures. Emphasis was put on investigating common features and differences across areas in the context of factors influencing multisensory integration. To do so, activity in response to unisensory visual (V) and auditory (A) as well as multisensory audiovisual (AV) stimuli were recorded looking at both extracellular single unit and local field potential signaling. Stimulus properties such as spatial location and stimulus timing were parametrically varied in line with the principles of multisensory integration. Traditional bimodal as well as modulatory interactions were evaluated and several key findings emerged which will be discussed in subsequent sections. Additionally to this, local circuit activity in cortex was characterized utilizing simultaneous linear multilaminar recordings and similarities as well as differences were delineated between a primary sensory field and an area within association cortex. Major findings will be discussed here (see section *a. Summary of results*) and put into context of general (multisensory) brain networks relating them to a few well-known multisensory phenomena. Subsequently, findings will be related to what is known about behavioral and perceptual processes, both in the healthy populations as well as in several clinical disorders. Throughout the discussion, points of future investigations will be made as they relate to the present findings and what is known in the field (see section *b. Implications of key findings*).

a. Summary of key results

The interrelationship of the principles of multisensory integration

All four data chapters revealed strong interdependences of the principal factors of multisensory integration. Data showed that temporal and spatial features of multisensory stimuli could modulate their effectiveness, which in turn is strongly shaping multisensory gain during those trials. Overall, this gain was visible in single neuron activity and in the local field potential (LFP) across cat subcortex and cortex, as well as in human performance. For example, superior colliculus neurons exhibited spatial receptive fields (SRFs), which were heterogeneous in nature showing regions of strong and regions of weak responses to unisensory and multisensory stimuli. The interplay between spatial location and the effectiveness of the stimulus was evident in how stimulus location affected multisensory integration. Here, stimulus locations that elicited weak responses under unisensory conditions showed the strongest gains under multisensory stimulation (see chapter 5). These heterogeneous SRFs were also observed in cortex (Carriere et al., 2008; Royal et al., 2009) and subcortex (Ghose & Wallace, 2014) suggestive of this being a general processing strategy of at least multisensory regions that deal with space.

Local field potentials measured in a sensory subfield of insular cortex, the anterior sylvian area (AS), and in primary auditory cortex (A1) further illustrated interplay between temporal and spatial stimulus factors as they modulate stimulus effectiveness.

In AS (see chapter 3), while audiovisual interactions generally resulted in significant changes in response magnitude, peak amplitude, and response latency, AV response magnitudes were highest for stimulus locations above and below the horizontal plane suggestive of some spatial specificity. A further breakdown by supragranular (SG), granular (G), and infragranular (IG) layer interactions revealed largest peak amplitude gains to be in IG layers for locations above the horizontal plane. Latency shifts in audiovisual response onsets were significantly reduced in layers I-IV, a phenomenon that held true for all tested locations. Varying the stimulus onset asynchrony (SOA) between the visual and auditory stimuli demonstrated that strongest reductions occur at short SOAs and even include lags where the auditory stimulus precedes the visual cue.

In A1 (see chapter 4), auditory LFPs differed with stimulus location in that locations above and below the horizontal plane elicited significantly weaker LFP peak amplitudes than locations in the horizontal plane. And indeed for those locations, visual LFPs significantly increased LFP peak amplitudes suggestive of interplay between spatial location of the stimulus and stimulus effectiveness. This result also implies some spatial specificity of the visual signal, as it was strongest in those locations where auditory was weakest. A breakdown by cortical layer further revealed that LFP peak changes occurred in supra- and infragranular layers omitting the presumed granular layer. A more detailed discussion of local circuit interactions will follow later.

An interrelationship between stimulus factors and the related principles of multisensory integration was further evident in a series of psychophysical experiments undertaken in healthy young adults (Nidiffer et al., 2015 (in revision); Stevenson, Fister, et al., 2012). The current thesis (see chapter 6) details that participants perceive audiovisual stimuli presented at a foveal stimulus location (0° azimuth at eye level) as synchronous over a wider temporal binding window (TBW, set of SOAs perceived as synchronous at least 75% of the time) during low saliency conditions, suggesting that the TBW is not a static construct but rather one that is dynamic and dependent on stimulus effectiveness. This further emphasizes that temporal stimulus properties and stimulus effectiveness co-modulate perception of multisensory events and thus illustrate some degree of interdependence. A similar widening of the TBW was observed when stimulus location but not stimulus saliency was varied with the widest TBW being found at the 90° peripheral location (Stevenson, Fister, et al., 2012). Further evidence of co-modulation was seen during the localization task where race model violations increased with decrease in saliency and a larger number of participants with violations were observed for peripheral locations (Nidiffer et al., 2015 (in revision)).

Multisensory integration in association versus primary cortex

Chapters 3 and 4 delineate audiovisual integration at the level of LFPs in association (insular, AS) and primary (auditory, A1) cortex. Stimulus conditions were the same between these areas in order to compare and contrast processing similarities and differences between AS and A1. Both regions showed robust auditory and visual LFPs across multiple layers. Audiovisual integration was seen in changes in peak amplitudes and latencies as well as response magnitudes and latencies. Often, AV signals demonstrated enhanced peaks and response magnitudes accompanied by a shift to shorter latencies. This was further modulated with stimulus onset asynchrony and stimulus location. Integration in auditory cortex was primarily restricted to supragranular and infragranular layers while in AS interactions were evident in all three divisions (SG, G, and IG). Striking differences between the two regions were found in the specificity of the signals. Visual modulations in A1 appeared to provide spatial content to the auditory cue as seen in strong modulations with stimulus location, particularly for locations outside the horizontal plane. Audiovisual interactions in AS were less strongly affected by spatial stimulation but showed strong effects on response onset by significantly reducing latencies in supragranular and granular layers.

b. **Implications of key findings**

The principles of multisensory integration revisited

Data from this thesis and other work call into question whether or not the principles should be considered as their own entities. As described in the introduction, they were traditionally studied in isolation, but emerging evidence suggests that stimulus factors greatly influence each other, which may simplify processing strategies of multisensory neurons. Interestingly here it appears that the principle of inverse effectiveness may be the governing principle as space and time might merely modulate stimulus efficacy. This is particularly evident in these multisensory hotspots described in chapter 5, which showed strong non-linear gains for stimulus locations that elicited weak responses under unisensory conditions. This may prove particularly relevant and beneficial when dealing with natural stimuli, which often feature complex spatial and temporal properties. These in turn may be able to modulate stimulus effectiveness separately or together and thus differentially affect multisensory benefits. One potential mechanism to process these complex aspects of natural stimuli may be through heterogeneous spatial and spatiotemporal receptive fields (SRFs, STRFs). Particularly, STRFs may provide a mechanism or architectural framework to merge spatial with temporal information of multisensory events. The following section will discuss potential functional roles within which processing through SRFs (and STRFs) may be particularly useful. These include but are not limited to binding multisensory stimuli, processing stimuli in motion, sensory coordinate transformation, as well as integrating information across ‘what’ and ‘where’ processing streams,

Facilitation of perceptual binding of multisensory stimuli across space and time

One important notion of processing multisensory events is that they need to be bound across space and time. This process may be accomplished through spatiotemporal receptive fields. Indeed, STRFs architecture would be uniquely suited to combine information across the senses and their spatial and temporal features to provide a more complete picture of an external multisensory event (Sarko et al., 2012). As discussed earlier, work looking at spatial determinants identified multisensory hotspots that show greatest gains when unisensory responses at the same location are weak. Research looking at temporal characteristics has focused on identifying differences in the temporal dynamics of multisensory integration and has revealed two key features: early superadditive responses, which are associated with response latency reductions (Rowland, Quessy, et al., 2007) and later interactions, which lead to increased discharge durations (Royal et al., 2009). Reduced latencies are thought of to bring about or contribute to speeded response times, a phenomenon that has also been associated with changes in local field potentials (see chapter 4) and changes in EEG signals (Molholm et al., 2002). Increased discharge duration or signal changes on the other hand may facilitate object analysis (Sarko et al., 2012). Thus, STRFs, showing both spatial and temporal effects, which in turn appear to modulate stimulus effectiveness, and bring about the strongest gains with the combination of weakly effective unisensory stimuli, may provide the ideal framework to merge spatial and timing information of multisensory stimuli. For example, a moving audiovisual stimulus will have spatially coincident auditory and visual component cues, moving at the same speed, in close temporal proximity. STRFs thus should show strongest multisensory gains for audiovisual stimuli that are in the same spatial location around the same time within a receptive field (and that are weakly effective on their own). This non-linear gain in turn may signal that two external unisensory events should be perceptually bound due to their spatial and temporal proximity as reflected in the neural response gain at the location of the multisensory hotspot.

Perceptual binding of multisensory events: interplay of bottom-up and top-down attention

Perceptual binding of multisensory stimuli often involves interplay between bottom-up stimulus driven and top down more cognitive events. What the individual contributions are remains to be solved but multisensory gains may be one way of (bottom-up) signaling the need to allocate top-down attention to a specific region within the receptive field. As seen in the current SC study (chapter 5), SRFs often feature one (or multiple) unisensory and multisensory hot spot(s), which are regions of strongest activity within the RF (Krueger et al., 2009). Changes in activity, and particularly strong non-linear gains at hotspots during multisensory integration may signal to distribute attentional resources to that specific location, which in turn may facilitate perceptual binding. In the preset data set, multisensory integration generally occurred at several stimulus locations but stimulus locations, which elicited weak unisensory responses, resulted in the largest response enhancements under multisensory conditions. Attentional allocation may be determined by monitoring relative changes in activity across the receptive field and having both unisensory and multisensory SRFs which are heterogeneous may be one underlying mechanisms to do so. Here, it would be interesting to determine how much stimulus driven attention and top-down attention contribute to multisensory gain and in turn to perceptual binding of multisensory events. Indeed, attentional modulations of neuronal activity have been demonstrated, for example in primate SC, where data showed visual spatial attentional effects in that neural firing was modulated when a cue and a target stimulus appeared within the RF but was not affected when the cue appeared outside the RF (Robinson & Kertzman, 1995) or when attention was covertly shifted to prior unattended locations (Ignashchenkova et al., 2004). If one would presume that bottom-up and top-down attention equally contribute, one could postulate that multisensory hotspot activity may modulate SC activity in a similar way to attentional shift. To measure that, an initial simple experiment where an animal has to detect for example a visual stimulus while measuring SC activity comes to mind. Conditions should include unisensory visual trials where the animal either gets cued or not, and multisensory trials where there is an additional auditory stimulus to the uncued visual one. Comparing multisensory trials with cued unisensory trials may delineate if multisensory integration shows comparable (or more) facilitation than attentional shift.

It seems unlikely that each attentional type contributes equally at all times. For example, one could imagine a scenario where attention is allocated to the central visual field, for example during foraging behaviors. In order for events in the periphery to capture attention and elicit an orientation behavior, they have to become salient to the system (i.e. bottom-up attention may need to be heavier weighed than top-down attention). Looking at spatial determinants of this may be a fruitful next step. In order to evaluate spatial factors, the previously described experiment could then be extended to include multiple stimulus locations with the same trial structures (cued and uncued visual as well as multisensory trials) with emphasis on peripheral locations or locations outside the horizontal plane. Data from current experiments (chapter 3 and 4) suggest that spatial locations outside the interaural plane often elicit the strongest multisensory interactions, which may be the underlying neural substrate supporting bottom-up attention reweighing. Here, unisensory alone stimulation often elicited weak responses and greatest gain was achieved under multisensory conditions suggesting that a relative change in activity in response to unisensory and multisensory stimuli may be more apparent or robust potentially resulting in alerting the system in a stimulus driven manner to allocate attention to those locations. Particularly, when thinking of sound localization for example, sounds located in the horizontal plane are easier to detect than outside of it and auditory cues alone may already be sufficient to properly locate the source of a sound. Thus the system would have the most to gain when the auditory system is least reliable (i.e. locations outside the interaural plane) and here the addition of a non-auditory cue may be the most beneficial and relevant and thus the system may be more susceptible to reweighing of bottom-up and top-down attention for those spatial locations. Of course, this experiment could be repeated in a host of other structures than SC as heterogeneous SRFs have been found in cortex and subcortex ((Carriere et al., 2008; Ghose & Wallace, 2014; Royal et al., 2009) and spatial factors have been found to be strong influences on multisensory integration not just at the single neuron level but also in small assemblies of neurons as measured via LFPs.

Motion processing

Another potential benefit of having heterogeneous SRFs may involve motion processing. Indeed, data from unisensory studies suggest that heterogeneous RFs aid in motion selectivity (visual (Clifford & Ibbotson, 2002) and auditory (Wagner et al., 1997;

Witten et al., 2006)). Specific brain regions or networks may do this by monitoring changes in neural activity as a stimulus moves through the RF (let’s say from low activity to hot spot to low activity) of a multisensory neuron or through the RFs of neuron assemblies. If this holds true in unisensory domains, then similar processing strategies would be expected for multisensory events and thus a hotspot may track a multisensory object in motion. Additionally, monitoring object motion in the unisensory domains and subsequently establishing whether or not they match in motion speed and direction can be a determinant of perceptual binding in general. This may be particularly useful with weakly effective unisensory stimuli.

For example, an enhanced response at a SRF hotspot may ultimately allow the detection of the stimulus events in an ambiguous context where visual cues may be occluded or auditory signals may be embedded in noise. The neural substrates for this may indeed lie within these non-linear changes as observed in multisensory hotspots, which appear to be strongly influenced by stimulus effectiveness. Here, in a noisy or ambiguous environment, unisensory stimulus effectiveness would be reduced, which should lead to the largest multisensory gains (see chapter 5) making the stimulus more salient to the system and potentially allowing for easier detection. A real-world example could be a car approaching on a busy street. Visual and auditory properties may be ambiguous at first as many cars are on the road, but having integrated audiovisual cues may lead to better (let’s say earlier) detection of the car and may aid in identifying the direction it is moving in.

Sensory coordinate transformation

Sensory coordinate transformation may also be mediated through heterogeneous SRFs. As discussed in the introduction, integrating auditory and visual cues often requires matching the receptive field properties of the constituent unisensory signals as they are coded in different native forms (head-centered versus eye-centered for instance). In support of that, data from primates elucidate that audiovisual RFs are frequently in an intermediate reference frame in order to promote integration (Schlack et al., 2005). Integrating multisensory stimuli through heterogeneous, flexible SRFs despite their constituent native unisensory receptive field forms potentially being different (Carriere et al., 2008; Krueger et al., 2009; Royal et al., 2009; Royal et al., 2010) may allow for easier transformation to a common reference frame and thus lead to easier cross-sensory binding. Findings from unisensory studies highlight that unisensory neurons often show a continuum of reference frames from eye-centric to head-centric to body-centric, particularly in regions of association cortex exhibiting multisensory processing (Avillac et al., 2005; Duhamel et al., 1997; McGuire & Sabes, 2011), and thus testing what reference frames characterize heterogeneous multisensory RFs may be a crucial next step. Here one could postulate that multisensory hotspots arise with shifting reference frames. This shift may cause regions of overlap to change creating locations that show weak unisensory responses, which are expected to show strong integration during multisensory conditions. Supporting that are findings from the same study that showed intermediate RF reference frames for multisensory neurons, which also demonstrated that at least the constituent unisensory RFs appear to be heterogeneous in nature (Schlack et al., 2005) hinting at a framework for a relationship between heterogeneity and sensory coordinate transformation.

In addition to evidence of a common reference frame, integration may also be influenced by predictions based on one modality over another (for example predicting the visual location of a stimulus given where it is felt on the skin (Avillac et al., 2005)) suggesting an interplay between common and native reference frames. Computational models further elucidate that shifting reference frames is dependent on network dynamics and connectivity, and may involve both, common reference frames and modality-specific predictions (Pouget et al., 2002). Having heterogeneous RFs may play a crucial role here as hotspots in the unisensory domain may serve as points of modality-specific predictions while multisensory hotspots may be indicative of coordinate transformation. Here it is noteworthy, that locations of unisensory hotspots generally do not overlap with locations of multisensory hotspots as weakest unisensory locations show largest multisensory facilitation (Carriere et al., 2008; Ghose & Wallace, 2014; Krueger et al., 2009) allowing the system to keep track of unisensory and multisensory information in a parallel manner.

Thus coding of modality-specific predictions may be linked to the location of the unisensory hotspots while large gains under multisensory conditions (i.e. multisensory hotspots) in the SRFs (see chapter 5) may highlight a transformation to a common coordinate reference frame as predicted by integration across modalities. This dynamic interplay between unisensory and multisensory SRFs may be one mechanism that combines these two aspects of sensory coordinate transformation as shown in modeling data. Nevertheless, a thorough investigation relating heterogeneity of the RF to modality-specific reference frames and predictions as well as characterizing how heterogeneity may influence a common multisensory reference frame remains to be done in the future. Furthermore, anatomical connections and features that give rise to such heterogeneous receptive fields need to be characterized in detail to make predictions on network interactions underlying sensory coordinate transformation.

Integration of “what” versus “where” information

Spatial and spatiotemporal RFs may be uniquely suited to combine information about spatial location as well as identity of an object or event. For instance, multisensory SRFs carry information of object identity (it being multisensory for example) and object location while STRFs additionally carry information about the temporal dynamics of the object. Furthermore, a potential role in motion processing would provide additional information such as predictions where the object will be in the near future. Multisensory heterogeneous receptive fields have been demonstrated in subcortex (Ghose & Wallace, 2014; Krueger et al., 2009) and cortex (Carriere et al., 2008; Royal et al., 2009) suggesting that they are a common feature of multisensory integration but may also contribute differentially depending on where they are found along the signal processing hierarchy (Sarko et al., 2012).

It is noteworthy here, that heterogeneous multisensory SRFs are not simply computational products of heterogeneity in unisensory SRFs, and instead multisensory response enhancements frequently exceed linear predictions. Indeed, this gain may be exactly what facilitates the identification of an object. A series of events could result from these response enhancements that may start with signaling that the object is multisensory in nature, followed by directing attentional resources toward it, which then leads to an orientation behavior for example. If the object is in motion, calculations leading to predictions of future locations may be undertaken simultaneously, with spatial and temporal information being integrated across these STRFs.

Altogether, this cascade originating in SRFs or STRFs may be one mechanism for integration across ‘what’ and ‘where’ streams. Yet, how exactly RF architecture relates to integration of ‘what’ and ‘where’ information across the senses remains to be investigated. Studies looking at ventrolateral and dorsolateral prefrontal cortex (VLPFC, DLFPC), which are both multisensory in nature (see chapter 1), identified these structures to be potential hubs for integrating both processing streams (Romanski, 2004; Wilson et al., 1993). Experiments here should initially target whether or not receptive fields show heterogeneity similarly to RFs in SC or lower level association cortices and if the RF architecture relates to informational content of the multisensory event. Location and feature-based analyses may subsequently give insight into potential integrative mechanisms within a multisensory receptive field corresponding to integration of information across sensory modalities.

Multisensory integration in the insula: functional implications

Audiovisual interactions in cat insula (chapter 3) encompassed changes in response magnitudes, peak amplitudes as well as latency shifts. While multisensory magnitude changes were generally subadditive and occurred across all layers, when multisensory responses were compared to the maximum unisensory responses some-spatial specificity was noted for stimulus locations above and below the horizontal plane. Nevertheless, the most striking interactions were evident in large reductions in LFP response onsets during audiovisual conditions. Furthermore, audiovisual facilitation was often limited to shorter stimulus onset asynchronies. These findings suggest that insular cortex may deal with temporally precise multisensory events and some implications will be discussed later.

Much headway has been made in identifying potential insular roles in perception and behavior with strong emphasis on integrating extero- and interoceptive information in relation to communication, emotions, and attentional processes (Nieuwenhuys, 2012). Relating multisensory processing to any of the roles or to integration of extero- and interoceptive cues remains to be investigated. Present findings are the first to systematically characterize insular activity at the neural level to audiovisual stimulation with varying spatial and temporal features. While no direct measures of behavior or perception were obtained along with neuronal recordings, a few speculations can be made.

Insula's contributions to body-ownership and integration of internal versus external cues also requires cross-sensory correspondence (Tsakiris, 2010). Coordinating across (personal) space and time for multiple senses in order to create a percept of oneself presumably deals with some degree of temporal precision as for example information from the eyes and skin may travel at different speeds than internal signals such as attentional processes or mood. Insula thus is tasked with keeping a temporal (and maybe spatial) representation of the speed of processing of internal and external cues in order to integrate appropriate signals. Present data (chapter 3) emphasize the importance of multisensory temporal dynamics as a predictor for multisensory integration in the insula. Findings in the current thesis for example suggest that latency reductions are restricted to short SOAs while longer SOAs are characterized by latency delays compared to the fastest unisensory response. This at the population level may shape temporal binding windows so that they are fairly narrow and only temporally precise multisensory information arriving in very short sequence of each other may be perceptually bound. Aforementioned in turn then may aid in creating better representations of external cues related to body-ownership as they occur near the body and signals would need little travel time. One may thus argue that allowing for little to no temporal disparity of sensory cues in this case is beneficial as it is restricting integration of information close to the body.

In line with this idea that insula my specialize in the integration of information arriving from personal space, are studies in humans delineating pain body maps in insula that showed clear somatotopy (particularly implicating face and upper torso and limbs) utilizing fMRI (Brooks et al., 2005; Henderson et al., 2007) or direct stimulation (Mazzola et al., 2009). Furthermore, data from one study investigating audiovisual stimulus onset asynchrony detection demonstrated strong PET activation of insular cortex (Bushara et al., 2001). Nevertheless, insula function has also been implicated in processing peripersonal or extrapersonal space information (Nieuwenhuys, 2012), which may require multisensory interactions to occur over a range of SOAs as it has been argued that this allows making up for the different traveling and processing speeds of unisensory signals. Data in chapter 3 illustrated that although response onsets with larger SOAs were significantly delayed compared to that fastest unisensory signal, they were still significantly different than a predictive model. This separation between onset facilitation compared to what is predicted and onset delay compared to the fastest unisensory response may be one mechanism to deal with stimuli from personal versus peripersonal versus extrapersonal space. Nevertheless, a more detailed exploration of temporal dynamics of multisensory stimuli at the single neuron level in insula is needed to shed light onto these differential processes.

Insula has also been linked to attentional allocation, saliency processing, and task switching (Menon & Uddin, 2010). Higher detection rates, increased accuracies, and speeded reaction times with multisensory stimuli may arise from multisensory events being more salient or capturing attention quicker than unisensory events, particularly if unisensory stimuli are ambiguous. Audiovisual events that are aligned in space and time are integrated in posterior insular cortex (see chapter 3) and are then potentially further integrated with internal cues along the posterior-anterior axis (see introduction chapter 1), which may result in an attentional shift. As alluded to earlier, heterogeneous spatial and spatiotemporal receptive fields may be one underlying mechanisms to facilitate attentional capture. While we did not specifically test SRF and STRF architecture in insula, spatial and temporal effects were observed. Thus, reductions in response latencies or response enhancements for various stimulus spatial locations under multisensory conditions as described in the present data may speed up such attentional allocation, which in turn could lead to speeded reaction times behaviorally. A next crucial step would be to indeed characterize unisensory and multisensory receptive field organization in insula, similarly to what has been done in other cortical and subcortical regions in cat (Carriere et al., 2008; Ghose & Wallace, 2014; Krueger et al., 2009; Royal et al., 2009). Following that, the effects of attention on multisensory processing in insula should be explored. This could be done in a similar way to what was proposed earlier in the discussion in SC. Correlating behavior and neural activity during cued and uncued unisensory and multisensory trials and subsequently comparing between these conditions might discern the contributions of attention to multisensory processing in insula. In order to better link behavior and insula activity, a set of for example optogenetic experiments could selectively active or deactivate regions within the insula. Identifying and characterizing deficits or gains associated with deactivation/activation of for example the posterior insula during a multisensory task (let’s say a simple detection task near and far away from the body for example) may shed light onto the contributions of multisensory processing to perception and behavior.

Contributions of modulatory interactions in primary auditory cortex to perception and behavior

Two prominent hypotheses have been proposed regarding the contributions of visual (and somatosensory) modulations of auditory activity to auditory cortex function. They encompass providing it with additional spatial information and readying it for newly incoming signals (Schroeder & Foxe, 2005). Both, somatosensory and visual representations are associated with strong spatial precision and thus having additional sensory information may allow for improvements of auditory spatial localization. This idea is supported by research in animal studies with 1) evidence from ferrets (Bizley & King, 2008), which showed that A1 and other auditory cortical fields gain spatial information with the addition of a visual stimulus to an auditory cue and 2) data provided in the current thesis. Indeed, audiovisual interactions in cat A1 were greatest and significantly different from auditory alone stimulation for locations where the auditory signal was weak and the visual signal was strong. This generally held true for all tested locations outside the horizontal plane. Such interactions were limited to supra- and infragranular layers suggestive of potential feedback interactions.

This may further be supported by significant latency shifts corresponding to times expected of feedback interactions (later than100ms after stimulus onset). Reaction times (RTs) during the audiovisual localization portion of the experiment described in chapter 6 (Nidiffer et al., 2015 (in revision)) would allow for visual feedback to auditory cortex as part of the neural pathway that supports localization behavior (Lomber et al., 2007; Rauschecker, 1998). Evidence from visual studies points out that visual attention effects as well as contextual information often rely on feedback mechanisms (for a review see (Schroeder, Mehta, et al., 2001)). Nevertheless, the present data (chapter 4) also suggests potential feed-forward interactions with latency shifts in granular layers. Thus, the exact contributions of feed-forward and feedback visual modulations and its effects on auditory localization need to be further characterized in the future.

One possible experiment here could include concordant laminar recordings in primary auditory cortex while an animal is subjected to an auditory localization task with and without the addition of a visual stimulus. Identifying laminar differences in activity (particularly latency differences) will allow inferences for potential thalamus and cortex contributions to these audiovisual interactions and can aid in establishing what contributions are of a feed-forward and what of a feedback nature. Moreover, taking advantage of anatomical knowledge identifying different brain regions that could send visual information to auditory cortex, selectively silencing visual feedback or feed-forward projections during the experiment, measuring performance and neural activity during the spatial task, and subsequently identifying (if any) behavioral deficits associated with specific silenced areas can further distinguish between both mechanisms.

Data from primates strongly imply that somatosensory cues may ready auditory cortex for newly incoming auditory signals by resetting ongoing oscillatory phases (Lakatos et al., 2007; Lakatos et al., 2005). Preliminary data from the same group also suggest that visual inputs can reset activity (Schroeder & Foxe, 2005). Although, the current experiments did not test for oscillatory interactions, data presented in chapter 4 indicate widespread visual modulations in A1, essentially spanning all layers. These broad input patterns may provide a good substrate to influence ongoing oscillations in a layer-specific pattern in the same way described in primates. Further studies should investigate oscillatory mechanisms of audiovisual interactions in cat primary auditory cortex in order to better elucidate the nature of these interactions and make predictions on perception and behavior. This should be undertaken in an awake, behaving preparation in order to avoid anesthetic confounds. An initial experiment could entail a cat being passively exposed to auditory, visual, and audiovisual stimulation while a multilaminar electrode is measuring neural responses across all layers. Stimulus locations should be parametrically varied in order to investigate if spatial influences are visible in oscillatory patterns similarly to what has been observed in the LFP signals in the current thesis work.

Comparing multisensory interactions in primary versus association cortex

The current thesis provides a laminar framework for multisensory interactions in primary auditory and association cortex in cat. A few similarities were noted. Generally, both regions showed strong audiovisual interactions across several layers as evident in response magnitude and response latency changes, particularly when unisensory responses were weak. These interactions appeared to be modulated by the spatial location of the stimuli as well as their temporal dynamics illustrating that the principles of multisensory integration appear to be universal processing strategies of multisensory neurons across the brain extending previous findings in cat from subcortex and association cortex to primary cortex. The present data also support the notion that these principles are interdependent with the principle of inverse effectiveness potentially being an overarching key principle. Interestingly, both structures implicated that multisensory interactions arise from interplay of information arriving from other cortical sources as well as thalamus with interactions spanning supragranular, granular, and infragranular layers, which will be discussed next.

Specifically, audiovisual interactions were visible in A1 and insula (area AS) in supragranular layers. For A1 recordings, they encompassed response peak enhancements for locations above and below the horizontal plane. In AS, interactions became apparent in response onset reductions and at first glance could be the result of integration of signals from extrastriate visual and secondary or tertiary auditory cortices. Nevertheless, response onsets in these laminae were at magnitudes associated with projections from thalamus. Particularly, audiovisual onsets were as fast as ~20ms implying that signals may stem from the suprageniculate nucleus, a multisensory thalamic input source to AS. This notion is further supported by the fact, that onset gains in insula were also observed for recording channels in the presumed granular layers. Suprageniculate projections are believed to primarily target layers I and IV. In A1, response enhancements most likely reflect interactions of auditory signals from medial geniculate nucleus and visual signals from extrastriate visual regions. Response onset gains were not observed.

As mentioned above, the presumed granular layer in AS showed response onset gains potentially arising from inputs from suprageniculate nucleus. In A1, however, peak latencies were significantly delayed, which would suggest that some multisensory transform might already take place in auditory thalamus, maybe in the medial division, which has been shown to have visual influences. With this potential extra step of processing including auditory information arriving in ventral MGN, being sent forth to medial MGN where some visual modulation takes place, and then being send on to the granular layer of A1, a delay of peak latencies is not unexpected. One may be able to postulate that in A1 response enhancements with the addition of a visual cue may be brought about in a trade-off with processing speed. Yet, when looking at the data irrespective of layer, peak latency shifts include onset delays when peaks occurred early in the signal and onset reductions when peaks occurred late in the signal suggestive of feed-forward and feedback processing mechanisms.

Audiovisual interactions in infragranular layers were not observed for AS but for A1 where they also appeared to be spatially influenced and selectively present for stimuli located above and below the horizontal plane.

Altogether, it seems likely possible that interactions in A1 in supra- and infragranular layers were mainly reflective of cortical visual feedback modulations while interactions in granular layers primarily arose from feed-forward thalamic interactions. In insula, the picture is less clear but response magnitude changes may have been brought about by corticocortical interactions while response onset reductions in supragranular and granular layers may be reflective of multisensory processing in thalamus.

On the nature of multisensory integration in cortex: feed-forward and feedback mechanisms

Studies in humans using event-related potentials (ERPs) have demonstrated early observable multisensory interactions over primary sensory cortices suggestive of feed-forward processing (Foxe et al., 2000; Giard & Peronnet, 1999; Molholm et al., 2002). Until then, based on evidence in humans and primates, it was widely accepted that multisensory interactions occurred in association cortex and unisensory regions may receive feedback from these multisensory fields (Felleman & Van Essen, 1991; Murray et al., 2002; Schroeder & Foxe, 2002). Yet, some multisensory benefits such as speeded reaction times during a detection task happen at timescales much faster than feedback interactions. Indeed one study showed that decreased RTs seen under multisensory conditions coincide with neural gains early in measured ERPs (Molholm et al., 2002)) providing a potential neural substrate for the observed behavioral benefits and indicative of early sensory cortices mediating such effects. Follow-up work highlighted both feedback as well as feed-forward multisensory interactions in primate auditory cortex (Lakatos et al., 2007; Schroeder & Foxe, 2002).

Behavioral and perceptual processes more than likely involve interplay between sensory bottom-up and higher-order, more cognitive top-down processes. As alluded to earlier, sensory and association cortices are pertinent to study such interplay as they receive distinct inputs to different layers allowing inferences of thalamic and cortical contributions as well as feed-forward and feedback connections. Analyzing laminar timing differences during multisensory processing will shed light onto potential mechanism differences. Chapters 3 and 4 begin to elucidate multisensory integration in local cortical circuits delineating characteristics of modulatory audiovisual interactions (as seen in A1) and traditional integration (as seen in AS). Interactions spanned all cortical layers and even suggested potential integration as early as thalamus as evident in interactions observed in granular layers. Furthermore, the data in A1 showed two distinct latency interactions (one early and one later), which may reflect feed-forward visual modulations of the auditory signal early and feedback interactions later.

Similar timing dichotomies have been observed in human ERP studies (Foxe et al., 2000; Molholm et al., 2002), which have been interpreted as early interactions in primary cortices and later interactions in traditional multisensory regions or interactions brought about by feedback signals to the early cortices. How exactly newly incoming feed-forward interactions are affected by feedback signals has yet to be determined and should be targeted for investigation in the future. Again, here auditory cortex (and other cortical regions) of the cat would be well-suited for study as the anatomical connections are widely established and cortical regions are easily accessible allowing for optimal electrode placement. This would also allow further characterizing potential processing differences between traditional multisensory integration (i.e. true bimodality) versus modulatory (or subthreshold) interactions and how they are affected by feed-forward and feedback interplay.

Multisensory integration in disease and disorders: implications of current findings

Many disorders such as schizophrenia, autism spectrum disorder, and dyslexia for example show changes in multisensory processing. These can be seen in alterations in integrative capacities such as decreased multisensory gains or failure to integrate multisensory cues (schizophrenia (Blau et al., 2009; Stekelenburg et al., 2013; Woynaroski et al., 2013), changes in processing of multisensory temporal features (Martin et al., 2013; Stevenson, Siemann, Schneider, et al., 2014; Virsu et al., 2003), as well as integration of unrelated or inappropriate cues (Brock et al., 2002; de Jong et al., 2010; Wallace, 2009). Many of these deficits have been linked to alterations of multisensory network activity, particularly in the temporal realm. The current thesis work highlights how intricate local network dynamics and how non-dominant sensory modalities can modulate ongoing activity even in a unisensory cortex. Both experiments, AS and A1, showed significant latency shifts under multisensory conditions which were often accompanied by a multisensory gain in the LFP signal. These phenomena, as discussed earlier, may be the underlying neural mechanisms to behavioral gains observed in human performance. Changes in these networks likely result in changes in behavior and perception. Although the current thesis work may be applicable to several disorders, the following sections will focus on autism spectrum disorder and hearing loss as both are extensively studied and very relevant to research focusing on multisensory integration.

Autism Spectrum Disorder

For example, brains of individuals with ASD show alterations in functional connectivity between thalamus and cortex (Nair et al., 2013) and between different cortical regions (Geschwind & Levitt, 2007; Just et al., 2004; Just et al., 2007; Minshew & Williams, 2007) as well as changes in cortical morphology (Casanova & Trippe, 2009; Girgis et al., 2007; Hutsler & Zhang, 2010; Raznahan et al., 2012; Raznahan et al., 2010) compared to age-matched controls.

Take for example, changes in multisensory thalamocortical and corticortical interactions, which can occur as early as primary sensory cortex. Evidence from this thesis (chapter 4) shows that audiovisual information may already arrive from thalamus to layer IV of A1, and that other multisensory transforms occur in layers II/III and V/VI. Changes in that circuit may have cascading effects along the processing stream and may affect a multitude of interactions. Some evidence suggests that early interactions underlie multisensory gains in simple detection tasks for example (Molholm et al., 2002). Having underconnectivity from thalamus to cortex or between cortical regions, as it is often described in ASD, may explain the lack of integration or the deficits in multisensory gains as seen in individuals with ASD, particularly in the temporal domain (a presumed underdeveloped, malfunctioning, or absent connection may delay relevant information).

Imagine a scenario like in ASD where underconnectivity influences how a system learns the statistics of the environment, in this case with delayed information. One could then postulate that a widening of the temporal binding window as has been shown in studies of ASD is needed in order to make up for the delayed signals and guarantee binding of multisensory stimuli (Bebko et al., 2006; de Boer-Schellekens et al., 2013; Foss-Feig et al., 2010; Kwakye et al., 2011; Stevenson, Siemann, Schneider, et al., 2014). This notion is further supported by findings in insular cortex (chapter 3), which showed that multisensory signals are often significantly different compared to their unisensory constituents over shorter stimulus onset asynchronies. Changes in anatomical and functional connectivity of insular cortex have been demonstrated in individuals with ASD (Ebisch et al., 2011; Uddin & Menon, 2009) and thus underconnectivity here may alter these integrative features to consistently include longer SOAs, which at a population level may give rise to widened TBWs.

Sensory loss: the case of deafness and cochlear implantation

To date, probably the most successful ‘brain-machine’ interface is the cochlear implant (CI). Although much research has been done looking at the perceptual benefits associated with CIs, such as improvements in speech comprehension (Moeller, 2000), little is known about the underlying neural architecture that supports such benefits. Most germane here is that multisensory processes have been identified as a crucial factor for the development of normal speech production and comprehension(Massaro et al., 1996; McGurk & MacDonald, 1976; Vatakis et al., 2008), and recent research has focused on multisensory processes in CI users (Schorr et al., 2005). In this study it was shown that children with CIs can utilize crossmodal signals to improve speech perception, even though the auditory signals derived from the CI are quite different than normal auditory cues. In addition, these data highlight a sensitive period for the development of reliable auditory-visual fusion, suggesting a peak period for the neural plasticity underlying this process. Other groups have shown that individuals with CIs often perform better during speechreading tasks than their age-matched hearing peers (Rouger et al., 2007).

Despite this evidence for enhanced multisensory processing in CI wearers, virtually nothing is known about the brain bases for these adaptive changes.

Studies have shown remarkable compensatory plasticity in neural systems, in particular when specific sensory inputs are eliminated (i.e. deafness (Meredith & Lomber, 2011; Meredith et al., 2011)) due to genetic or environmental factors. After re-introduction of the missing sensory information (i.e. CI fitting), the brain subsequently can adjust again to process this novel sensory information, resulting in the restoration of some degree of sensory function. How the brain reorganizes to effectively utilize these newly experienced sensory signals remains largely unknown. Plasticity of the auditory cortex in deaf animals after cochlear implantation has been studied extensively and data indicate that cat auditory cortex is capable of substantial reorganizational change (Klinke et al., 1999; Kral et al., 2002). To date this work has been largely focused within sensory systems (i.e., audition), despite the well-established links between audition and vision from processes such as speech comprehension.

The current thesis work (chapter 4) highlights that already primary auditory cortex processes substantial multisensory information. Indeed, audiovisual signals were actively integrated and were modulated depended on cortical layer and stimulus location. As discussed in chapter 4, similar phenomena have been observed in other species (primate (Hackett & Schroeder, 2009; Murray et al., 2012; Schroeder & Foxe, 2004) and ferret (Bizley & King, 2008, 2009)) suggesting this likely being a general feature of auditory cortex. Furthermore, the present data and data from other labs (Foxe & Schroeder, 2005; Ghazanfar & Schroeder, 2006; Lakatos et al., 2007; Murray et al., 2005; Schroeder & Foxe, 2002; Schroeder & Foxe, 2005) suggest a multi-faceted interplay between feed-forward and feedback mechanisms in early cortices undoubtedly shaping perception and behavior (Kajikawa et al., 2012; Lakatos et al., 2009).

How these networks are affected by sensory loss and potential hearing restoration remains to be investigated. Although, one may presume that having other sensory inputs to auditory cortex could be beneficial during hearing loss as plasticity may compensate quickly for lack of sensory input, the effects of this on hearing restoration are not clear. Thus future studies should characterize the consequences of deafness and of restored hearing on cortical multisensory processes, with the overarching view that multisensory plasticity plays an important role in the appearance of a functional auditory representation. Utilizing the present data as a backdrop to this may shed some light onto potential compensatory mechanisms and their utility during therapy after CI placement.

c. Conclusions

The present thesis set out to investigate multisensory processing across different brain structures spanning subcortex, primary sensory cortex, and association cortex. Emphasis was put on characterizing potential common processing features as well as highlighting differences in integration. The data suggests that one common feature of multisensory integration is the interdependence between stimulus factors as described in the principles of multisensory integration. Here, spatial and temporal features of multisensory stimuli modulate their effectiveness, which in turn shapes multisensory integration. Current data also illustrates that multisensory interactions are visible at the local field potential level showcasing substantial changes in response magnitudes and latencies. Furthermore, while primary and association cortices both integrate audiovisual information, they often do so differently particularly in context of activity within specific layers. Insular cortex appears to integrate audiovisual signals in a manner that suggests strong temporal processing preferences while modulatory interactions in primary auditory cortex may provide contextual cues such as spatial information in addition to information derived from the dominant modality. While, many questions remain to be investigated, the current work is an important first step in elucidating the contributions of multisensory processes to local and global network activity as it relates to perception and behavior.

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