424 R&R and PHS-398 Specific
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PI: **WALLACE, MARK Thomas**	Title: Multisensory Processing Across Lifespan and Links to Cognition	
	FOA: EY13-001	
	FOA Title: BASIC BEHAVIORAL RESEARCH ON MULTISENSORY PROCESSING (R21)	
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	Organization: VANDERBILT UNIVERSITY MED CTR	

RESEARCH & RELATED Other Project Information

1. * Are Human Subjects Involved? ☒ Yes ☐ No

   1.a. If YES to Human Subjects

   Is the Project Exempt from Federal regulations? ☐ Yes ☒ No

2. * Are Vertebrate Animals Used? ☐ Yes ☒ No

3. * Is proprietary/privileged information included in the application? ☐ Yes ☒ No

4.a. * Does this project have an actual or potential impact on the environment? ☐ Yes ☒ No

5. * Is the research performance site designated, or eligible to be designated, as a historic place? ☐ Yes ☒ No

6. * Does this project involve activities outside of the United States or partnerships with international collaborators? ☐ Yes ☒ No

Project Summary

The long-term objective of the proposed work is to provide the first comprehensive view of how multisensory function changes across lifespan. Emerging literature suggests a surprisingly long development process leading up to the mature multisensory state, and intriguingly that multisensory function in later life may compensate to some degree for age-related loss of acuity within the individual senses. In addition to being the first project to detail these changes across lifespan, the work will provide important windows into individual variability in multisensory function, and how certain domains of multisensory function map onto other domains (e.g., spatial vs. temporal function). Finally, the work seeks to detail relationships between multisensory abilities and higher cognitive processes, given that cognition is grounded in both the integrity of the information contained within the incoming sensory streams and the integration between these streams. The experimental approach will employ a sophisticated battery of tasks to assess ands relate multisensory and cognitive function. The proposed studies are oriented around two specific aims. The first is to characterize multisensory function in individuals ranging in age from 5 to 85. The second is to relate performance on our battery of multisensory tasks to performance on well-established cognitive tasks that index domains such as attention and working memory. Collectively these studies are predicated on the framework that multisensory function will change in systematic ways across lifespan, and that these changes will have important relationships to cognition. The **significance** of work lay in its potential to establish these relationships, which will have important implications for furthering our understanding of the maturation and aging of perceptual and cognitive representations – issues of powerful public health relevance from both the normal and clinical perspectives. The **innovation** of the work lay not only in the conceptual realm in being the first to systematically address these questions, but also in the technical realm in building a sophisticated battery of (multi)sensory and cognitive tests to explore age-related changes in each as well as their interrelationship.

Project Narrative

The proposed research seeks to characterize multisensory processing across lifespan, studying individuals from ages 5-85. The work will employ a battery of psychophysical tasks to assess multisensory function and its relationship to cognitive abilities, with an emphasis on individual differences as well as on correlations across the various tested domains. The overarching goals of the project are to better understand how multisensory abilities change across lifespan, and to gain critical insights into how multisensory processes shape cognition and cognitive capacity.

Facilities and Other Resources

Laboratory (Psychophysics)

At Vanderbilt, the PIs laboratories for conducted human psychophysical research are located in Medical Research Building III (MRB III) and in Medical Center East (MCE). The lab in MRBIII is approximately 750 sq. ft and is divided into a number of workstations for both data acquisition and analysis. The centerpiece of the lab is a pair of sound-attenuated enclosures (Whisper Rooms), within which participants will sit during the performance of the psychophysical tasks. Each of these rooms is outfitted with a high-resolution video monitor and headphones for stimulus delivery, and with a keyboard and response box. In addition, rooms are monitored with an infrared camera and intercom system. Adjacent to each of these rooms is a workstation used to control the experiment and to monitor participants. Additional workstations for performing data analyses are located in these labs. The lab in MCE is typically used for clinical populations, and will be adapted for the older participants, because of its ease of access for patients accessing hospital services. The lab here is approximately 250 sq. ft. and is made up of a single sound attenuated enclosure as described above. All of the associated equipment with this room is as described for the MRBIII laboratories. All of the psychophysical testing and training will be done in one of these laboratories.

Clinical

Vanderbilt Institute for Clinical and Translational Research- Clinical Research Center (CRC): Laboratory/ECG testing and some cognitive testing will take place on the Clinical Research Center (CRC). The Clinical Research Center, funded by the NIH/National Center for Research Resources provides inpatient and outpatient space, hospitalization cost, laboratories, equipment, nursing and supplies for clinical research. Clinical Research Center (CRC) use is justified by research quality and significance, need for common facilities, and common usefulness or collective justification for facilities or personnel. The CRC is available to investigators from all disciplines and departments at Vanderbilt and Meharry Medical Center and to research subjects of all ages. The center includes 21 inpatient beds and 7 outpatient rooms. Scientific facilities include an assay development laboratory, a body composition and energy balance laboratory, a bionutrition unit with metabolic kitchen, energy and nutrient intake assessment capabilities, a locked medicine room, a specimen procedure room, centrifuges, and freezers for temporary sample storage. A patient waiting room and dining facilities are available for all scientific projects.

Computer

Much of the necessary computing resources are in place at Vanderbilt University (many of which are described in the narrative above), outside of those that are specifically requested in this proposal. All of these machines are fully networked for ease of data transfer. In addition, a number of Macintosh and PC platforms are available for image analysis, graphics and word processing in the PI's laboratory.

Office

Dr. Wallace's office is located in MRBIII, and is immediately adjacent to the space used by postdoctoral fellows, graduate students and technical staff. In addition, all off-line data analysis workstations are housed in this space.

Other

A host of additional support facilities are provided by Vanderbilt University, the Department of Hearing and Speech Sciences and the Vanderbilt Kennedy Center. These include a number of core facilities, as well as secretarial, administrative and grant support services, a machine and electronics shop, computer support, graphic design, etc.

Equipment

All of the major equipment needed for the completion of these studies is currently in place at Vanderbilt University, except for the requested addition of a Whisper Room that can be dedicated to this experimental series. Major equipment for these projects is listed in the following narrative. For additional detail on the use of this equipment, please refer to the facilities and other resources section.

Sound attenuated testing chambers

All psychophysical testing and training will take place within a sound-attenuated enclosure (Whisper Room). These enclosures are fully outfitted with all of the equipment needed for displaying stimuli (video monitors and headphones), recording responses (response boxes and keyboards) and monitoring attention and motivation (closed circuit infrared TV camera, two way intercom). In addition, each room's environment is controlled from an external workstation, manned by laboratory personnel and that generates stimuli, logs responses, etc. Each of the multisensory tasks employed here can be structured within this environment, including the spatial localization tasks that necessitate pointing judgments to denote perceived target location.

Cognitive testing

All of the equipment needed for the cognitive battery is already in place in the Center for Cognitive Medicine, and which administers and scores these tests on a regular basis.

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OMB Number: 0925-0001

1. Project Director / Principal Investigator (PD/PI)

Prefix:
* First Name: Mark
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* Last Name: Wallace
Suffix:

2. Human Subjects

Clinical Trial? ☒ No ☐ Yes

* Agency-Defined Phase III Clinical Trial? ☐ No ☐ Yes

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4. Human Embryonic Stem Cells

* Does the proposed project involve human embryonic stem cells? ☒ No ☐ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://stemcells.nih.gov/research/registry/. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s): ☐ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

PHS 398 Research Plan

1. Application Type:

From SF 424 (R&R) Cover Page. The response provided on that page, regarding the type of application being submitted, is repeated for your reference, as you attach the appropriate sections of the Research Plan.

*Type of Application:

☒ New ☐ Resubmission ☐ Renewal ☐ Continuation ☐ Revision

SPECIFIC AIMS

Our world is made up of a wealth of information from a number of distinct sensory modalities – a multisensory mélange that we seamlessly integrate into a coherent perceptual unity. Despite the great advances that neuroscience has made in understanding how sensory information from the individual modalities is processed and how it influences our behaviors and perceptions, our knowledge of how sensory information from the different modalities is ultimately integrated in order to guide behavior and shape perception has lagged behind. This knowledge gap is rapidly shrinking as a host of studies have revealed multisensory-mediated improvements in behavior and perception. Collectively these studies have underscored the enormous adaptive value of having information available from multiple sensory channels, and in which behavioral responses and perceptual reports often differ dramatically from what one would predict based on the individual sensory cues.

To date, this body of work has focused largely on adults, and has provided an important framework from which to better understand multisensory synthesis and its contributions to the creation of our perceptual gestalt. In contrast, surprisingly little is known about how multisensory function changes across lifespan, including how it matures during early life and how it changes in later life when acuity within the individual senses declines. In an effort to fill this void, our laboratory, which has focused on questions of multisensory development and plasticity in animal models for many years, has recently extended our studies to begin to examine similar questions in children. These preliminary studies have revealed dramatic developmental changes in certain multisensory domains – changes that extend surprisingly late into adolescence. Our goal here is to build off of this exciting preliminary data. At the other end of the lifespan, very little is known about how multisensory function changes during normal aging. This question is of great interest given the age-related declines in the function of the individual sensory systems – declines that could result in substantial deficits in multisensory function because of its dependency on the individual sensory systems, or that could result in paradoxical *gains* in multisensory integration because of a greater compensatory reliance on cue combination. Regardless of the results, this would be one of the first systematic explorations of multisensory function in aging, work that could represent an important building block for the development of tools/strategies to improve healthy (and pathological) aging.

Although characterization of multisensory function across lifespan is in itself of great relevance, our view is that these changes will also have important implications for higher-order cognitive function. This hypothesis is grounded in the simple (but to date untested) idea that the information within the incoming sensory streams, as well as the integration across these streams, represents fundamental building blocks for the perceptual representations within which cognitive processes are grounded. Hence, individual variability in (multi)sensory function, along with changes in these functions across lifespan, are expected to map onto cognitive processes such as attention, memory, and executive function. The experiments outlined in the current proposal would be the first to test this question. Collectively, our proposal is built around two straightforward specific aims.

Aim 1: To characterize changes in multisensory function across lifespan.
This aim will explore multisensory function in individuals from ages 5 to 85 using a battery of behavioral and perceptual tasks already in place in our laboratory and that assess various facets of multisensory processes.

Aim 2: To relate multisensory function to performance on cognitive tasks.
This aim will relate performance on our multisensory battery to performance on well-established measures of cognitive function, with a focus first on individual variability in multisensory function and its correlations with cognitive measures, and second on examining age-related changes in the mapping between these domains.

The importance of these studies for public health cannot be underestimated. First, the lifespan questions will fill an important void in our understanding of age-related changes in (multi)sensory function, work of critical importance for better understanding developmental disabilities in which (multi)sensory processes are altered (e.g., autism, dyslexia), and for gaining a clearer picture of normal sensory aging and compensatory strategies that may improve quality of life in the elderly. Age-related declines in vision and hearing are an enormous public health burden, and little is know about how the interactions across these sensory systems change with age. Second, the work will be the first to map multisensory function onto cognitive performance, and holds promise for the development of multisensory training tools that may be co-opted to improve cognitive function. Although the scope is clearly ambitious, the goal of this project is simply to provide a strong foundation of preliminary data; data that we hope will represent the springboard for future more comprehensive studies.

SIGNIFICANCE

The utility of multisensory processes

We live in a world in which we are inundated with sensory information. Despite the fact that the sensory systems have unique receptor organs and processes for transducing the different forms of energy within which their information is encoded (e.g., photoreceptors in the eye, mechanoreceptors in the ear and skin, etc.), as well as dedicated lines to initially bring information into the brain, we perceive the world as a unified perceptual experience or gestalt. Consequently, one of the major challenges for our brains is to build an integrated perceptual representation – one that must “bind” items that belong together while segregating items that do not. Along with building unified perceptual representation(s), multisensory integration has been shown to alter behavior and perception in important and adaptive ways. One of the simplest examples of this can be seen in reaction times, where the pairing of visual and auditory cues results not only in faster responses than to either of the sensory modalities alone, but faster responses than those predicted by probability summation [1-8]. Other examples include improvements in target detection and localization [9-11], as well as a host of perceptual benefits including enhanced speech comprehension [12]. In recent years, there have been a number of studies detailing the behavioral and perceptual consequences of multisensory pairings, as well as numerous studies attempting to detail the neural bases of these effects (see [13-16] for reviews). *Collectively, this work has highlighted the dramatic influences that can be seen in the behavioral and perceptual domains, and which reinforce the biological and ethological significance of multisensory interactions.*

The development of multisensory processes

Although there has been a great deal of work characterizing the behavioral and perceptual consequences of multisensory stimulus combinations, this work has largely been restricted to adults. Only a limited number of studies have sought to extend these questions into the developmental realm, with most restricted to the period soon after birth (see [17] for review). Indeed, these studies have highlighted that multisensory processes at the earliest ages are strikingly immature. This has created a knowledge gap in our understanding of how multisensory function matures in children for ages leading up to adulthood. Our lab has a unique perspective on this question, in that we have spent a number of years examining the development and plasticity of multisensory processes in animal models – work that has illustrated that multisensory systems undergo a prolonged period of postnatal maturation characterized by enormous plasticity [18-21]. Based on these findings, we have recently extended our work into children, where we have made a preliminary effort to characterize aspects of human multisensory development [22, 23]. Of greatest interest in the current context is that this work has revealed that certain multisensory processes are still immature well into adolescence (fig. 1), reinforcing the need for a more comprehensive study examining the full chronology of multisensory development. *The significance of this work is in several realms. First, as highlighted, it would focus on filling the knowledge void concerning multisensory processing between infancy and adulthood. Second, because multisensory processes represent the critical foundation upon which perceptual and cognitive representations are constructed, a better view of their development would shed great light on the maturation of higher order processes. Finally, with the emergence of evidence that multisensory dysfunction accompanies developmental disabilities such as autism and dyslexia [24-34], a better understanding of the normal developmental trajectory for multisensory function will provide an important foundation for comparison.*

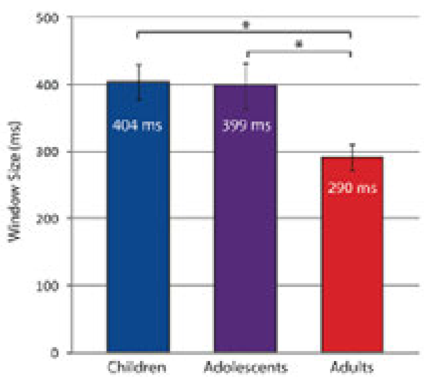

Figure 1. *The multisensory temporal binding window for simultaneity judgments remains immature into adolescence. Adapted from Hillock-Dunn and Wallace 2012.*

Multisensory function and aging

The aging process is accompanied by nearly inevitable declines in sensory acuity. Some of the more obvious examples of this can be seen in vision and audition, where visual acuity decreases and hearing thresholds increase in an age-dependent manner [35, 36]. In contrast, evidence for age-related changes in multisensory function has been surprisingly equivocal, with examples of declines, improvements, and no difference [37-48]. The inconsistency of these results is likely due to both task and population differences, since many of these studies employ complex cognitive tasks and individuals with and without cognitive impairments. In attempting to address these interpretational concerns, several more recent studies have demonstrated marked enhancements in multisensory function in older adults [44, 45, 48]. In this work, multisensory-mediated improvements in simple reaction times (RTs), saccadic RTs and audiovisual discrimination were found to be greater for older when compared with younger individuals. Although intriguing, particularly from the perspective that multisensory stimulation may be able to compensate for declines in individual sensory function, these studies provide only a few snapshots into how multisensory processes may change in the aging brain. *The significance of the work described in the current proposal lay in its ability to greatly extend our understanding of how multisensory function changes in aging, with the view that these changes will provide an important foundation upon which to interpret (and possibly even remediate) changes in cognitive processes*.

The relationship between multisensory function and cognitive processes

As alluded to above, one of our key hypotheses is that multisensory function and cognition are intimately related, a view founded in the idea that higher-order processes are critically dependent not only on the integrity of the information from the incoming sensory streams, but also on the rapid and accurate integration of information across the different sensory systems. Despite the seemingly intuitive nature of this prediction, surprisingly few studies have attempted to address the relationship between multisensory function and cognition. This is in spite of studies that have found links between unisensory (i.e., visual, auditory, tactile) function and cognitive processes; links that appear to strengthen later in life [49-52]. Our view is that these relationships between sensory function and cognition will be much stronger when considering the integration of information across the different sensory modalities. Further support for potential links between multisensory function and cognition come from a number of studies that have explored interactions between specific subdomains of each. For example, work has looked at how attention and multisensory function are related, and have established bidirectional interactions between them [53-57]. Similarly, multisensory influences on learning and memory are well established [58-60]. Evidence from clinical populations provides further insight, such as those that have shown strong links between multisensory function and language comprehension in autism [61, 62]. Despite these intriguing observations, no clear more global picture of how multisensory and cognitive processes are interrelated has emerged, and how these interactions change in aging. *Consequently, the overall significance of the proposed work lays in its employment of a battery of tasks that index various aspects of both multisensory and cognitive function, and in its focus on exploring the relationship between them within individuals and across lifespan.*

INNOVATION

We believe that the proposed studies are highly innovative from a number of key perspectives. Although many of these innovations are closely aligned with the significance highlighted above, we include the following bulleted points to emphasize the major innovative aspects of the proposed work.

- The work would be the first to focus on the development of multisensory processes in children between the ages of 5-21, ages at which dramatic changes in behavior, perception, and cognition are taking place.
- The work will employ a sophisticated battery of psychophysical and perceptual tasks to characterize how the stimulus factors of space, time and effectiveness influence multisensory interactions throughout lifespan.
- The work will be the first to detail individual variability in multisensory behavioral and perceptual function.
- The work would be the first to systemically examine how multisensory function changes with normal aging.
- The work would represent the first that attempts to systematically relate how multisensory function maps onto higher cognitive abilities, with an emphasis once again on individual variability.

APPROACH

Aim 1: To characterize changes in multisensory function across lifespan.

<u>Rationale:</u> As highlighted above, there is a rapidly growing body of work detailing the impact of multisensory stimulus combinations on behavior and perception. Much of this work has been done in young adults, leaving a critical gap in our knowledge of how multisensory function changes at either end of the lifespan. Studies of infants show a striking immaturity in basic multisensory processes [17, 63-70], our own preliminary studies suggest a very long maturational timeline for the establishment of adult multisensory function [22, 23], and we (and others) have found paradoxical improvements in multisensory abilities in later life [44, 45, 48]. Together,

these studies suggest substantial changes in multisensory function in young and old individuals; changes that are interesting not only for the window they provide into multisensory processes, but that we believe have important implications for cognition (see aim 2). Hence, our goal for this first aim is to conduct the first characterization of multisensory behavioral and perceptual function using a battery of tasks for participants ranging in age from 5 to 85. In addition to providing a view into how the various facets of multisensory function change across lifespan, the work will explore inter-individual correlations across each of the measured domains. Our own studies [10, 26, 71-78], along with the work of others [7, 8, 11, 42, 48, 58, 59, 79-92], has suggested that there is enormous variability from individual to individual in their performance on multisensory tasks, but the consequences of such variability remain unknown and unexplored. Consequently, the correlations that will be revealed in the current work will be of great importance not only in elucidating links between different facets of multisensory function (e.g., spatial vs. temporal, etc.), but also in providing a critical foundation for future work designed to examine the neural substrates for multisensory processes.

Participants: Vanderbilt University has access to multiple pools of potential participants for this aim, as well as significant expertise in testing children in psychophysical paradigms. Children will be recruited through the Vanderbilt Kennedy Center and the Department of Hearing & Speech Sciences, both of which have an extensive database of typically-developing (TD) children. Young adults will be recruited through standard means already in place in our laboratories. Older adults will be recruited through the Center for Cognitive Medicine, directed by one of the PIs (Newhouse). For the developmental phase of this work, children will be recruited from ages 5 and up, and subject numbers will be equivalent in the following age groups (5-8, 9-12, 13-16, 17-20). Power analyses structured on our preliminary data suggest the need for a total of 40 children (10 per age group). In addition, 20 individuals ranging in age from 21-65 will form the younger adult participant base, and 20 individuals between the ages of 66-85 will form the older cohort. Exclusion criteria include a history of neuropsychiatric illness, developmental disability (including reading disabilities) or cognitive dysfunction. All participants will have their vision and hearing assessed through standard optometric and audiometric tests (which will be factored into our analyses of multisensory function). We must reinforce that participant numbers are dictated by the R21 mechanism, and are designed to provide a strong preliminary dataset on an innovative idea that will shed critical light on the direction of future inquiries and analyses.

Methods and Analyses: Our laboratory has developed and refined a battery of psychophysical tasks structured to examine various aspects of multisensory behavior and perception. Many of these are modified from existing paradigms, and have been used repeatedly, and thus will only be described briefly. The battery can be completed in approximately two hours (generally divided into two sessions). The first class of tasks is **general tests** of multisensory function. The first of these is a simple reaction time task in which participants respond, via button press, as quickly as possible to an auditory target, a visual target or a combined audiovisual target. Prior work in adults has shown that paired audiovisual stimuli result in significant speeding of reaction times, and that these speeded responses exceed race model predictions, providing strong evidence for interactions across sensory systems [3, 93-96]. Furthermore, interesting age-related differences in multisensory performance have been seen using this task [44]. The second task will be an audiovisual discrimination task in which subjects report on the color of a target stimulus that can be specified in the auditory, visual, or audiovisual modalities. Again, we have preliminary data from this task suggesting interesting differences in aging [45]. Finally, we will use a standard speech-in-noise task to quantify the degree of information gain attributable to having access to audiovisual information [83, 89, 97-103]. In these speech-in-noise tasks, identification of target syllables and words is carried out while varying the signal-to-noise ratio.

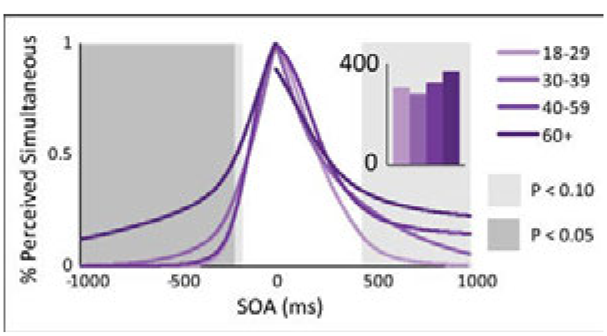

Figure 2. *Preliminary data from four adult age groups supporting an age-dependent widening of the multisensory temporal binding window.*

The second set of tests are **temporal** tasks, designed to evaluate how the temporal structure of paired visual and auditory stimuli alters psychophysical judgments. *Direct* measures of multisensory temporal perception include a temporal order judgment (TOJ – "Which came first?") [104-106] and simultaneity judgment (SJ – "Were the audio and video synchronous?") [77, 107]. Each task will employ audiovisual presentations with variable stimulus onset asynchronies (SOAs) ranging from 0-500ms including both audio and visual leading conditions. In addition, unisensory controls for each of the tasks will be conducted in order to test for the specificity of the multisensory effects (i.e., are they beyond those predicted from unisensory performance?). As an example of a unisensory control, for the SJ task, dual visual and dual auditory stimuli will be employed (differing in spatial location [visual] or ear of delivery [auditory]). We routinely employ such unisensory controls in our work. Each task will be performed using stimuli ranging from simple (flashes and beeps) through complex non-speech (dynamic tools) to speech (single phoneme utterances), thus providing a total of 6 direct measures of multisensory temporal perception. All pairings with semantic content (i.e., dynamic tools and speech) will be congruent. For each task and stimulus type, accuracy and response times will be measured, with accuracy being used to create a response distribution from which a proxy measure for the multisensory temporal binding window can be defined [77]. Figure 2 shows preliminary data from the SJ task supporting age-related increases in the width of the temporal binding window in adult subjects. In addition to these direct tasks we will include two *indirect* tasks, the McGurk effect [108] and the sound-induced flash illusion (SIFI) [109]. Synchronous versions of these tasks will measure the magnitude of audiovisual integration (i.e., the more illusory percepts, the stronger the integration), and asynchronous presentations using varying SOAs will be used to delimit the temporal binding window. Intrasubject correlations across each of the measured domains and tasks will also be examined.

The final tests are **spatial** tasks, designed to evaluate how multisensory interactions change as a function of the spatial location and spatial relationship of the paired visual and auditory stimuli. These tasks will explore a number of facets of multisensory spatial function, including: 1) improvements in the *detection* of spatially-concordant audiovisual stimuli, 2) improvements in the *localization* of spatially-concordant audiovisual stimuli, 3) spatial biases in the localization of spatially-discrepant audiovisual stimuli, and 4) unity judgments (i.e., "did the visual and auditory stimuli come from the same source?") based on the spatial location and relationship of the paired stimuli. The first task is an audiovisual detection task. Here, using signal detection analyses, as we have done in the past, we will explore how spatial location and proximity modulates the well-established improvements in detection seen with spatially-concordant audiovisual stimuli [10, 85, 110-114]. We will determine how spatially distant the auditory and visual stimuli can be for improvements in detection to be seen, providing a single metric for each individual (a secondary metric here will be magnitude of the gain). The second task will be an audiovisual localization task in which audiovisual pairs can be spatially-concordant or spatially-discrepant by varying degrees. Three important metrics will be derived in this task. The first will be improvements in localization for spatially concordant stimuli. The second will be bias factors that quantify the spatial influence of each modality on the other (see [78, 115-121]). The third will be a unity judgment that quantifies the threshold spatial separation necessary for subjects to report the stimuli as separate events [78]. As for the temporally-based tasks, these tasks will employ three types of stimuli (simple, complex non-speech and speech) as well as the requisite unisensory controls.

As highlighted above, each of these tasks is designed to provide a single (or in several cases multiple) metric of multisensory function for each individual. In addition to allowing us to chart changes in the various aspects of multisensory processing as a function of age at the population level, these values will be used to evaluate individual variability in multisensory function, as well as to examine how closely correlated the different measures are to one another in a given individual. Aim 2 describes these correlations in more detail.

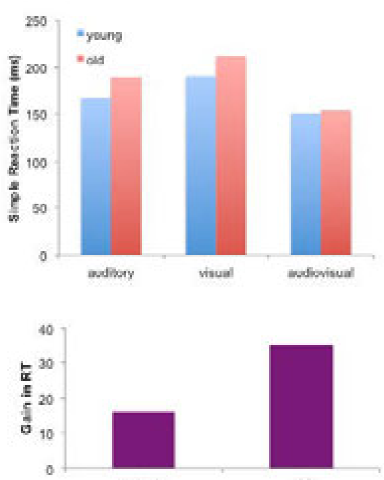

Figure 3. *Simple RTs for a small cohort (n=5 each) of younger and older adults (top). Note the greater multisensory improvements in RT in the older group (bottom).*

Hypotheses and Predictions: **The central developmental prediction is that multisensory function will mature dramatically from age 5 to adulthood.** This will be evident as increased multisensory gains in each of the tasks as maturation progresses. For example, we expect age-dependent decreases in simple reaction times to unisensory stimuli coupled with increased multisensory facilitation (i.e., greater speeding). In the spatial and temporal tasks, we also expect to see greater spatial and temporal specificity. Thus, the spatial extent of the multisensory effects are expected to decline with age, as is the temporal window within which multisensory stimuli are perceptually bound – both reflecting a "tuning" in multisensory perceptual representations. Finally, we expect that the development of multisensory function will proceed hierarchically, with the processes underlying the integration of simple stimuli maturing before those for more complex stimuli. **The primary prediction for the older subjects is a greater reliance on multisensory cues as acuity in vision and audition declines.** This is expected to manifest as greater proportional improvements on each of the tasks, and widened spatial and temporal integration windows. Figure 3 provides some preliminary data concordant with our expectations for the simple RT task. Finally, we expect that although there will a great deal of individual variability in each of the multisensory measures (in itself a widely understudied phenomenon), there will be strong correlations within individuals across these measures, likely reflecting a common underlying set of perceptual operations that bind stimuli across audition and vision.

Limitations, Caveats and Future Directions: The power of the tasks described above is that each has been well-established in adults in providing important information concerning multisensory processing, and a subset of these have been carried out in both young and old populations in preliminary work. Furthermore, the battery has been designed so that it can be completed over a timespan of approximately two hours. Hence, we have great confidence in the feasibility of the proposed study. One important note is that the developmental studies may entail customizing the tasks so that they are age appropriate. We have experience with such adaptations, as prior work in our lab has embedded our tasks within age appropriate games for children [22, 23]. One significant potential concern of the proposed work is its ambitiousness and the limited number of subjects. We recognize this concern, but argue that the data that will be gathered and its insights into multisensory processes will be foundational for future studies that seek to characterize these issues in greater detail.

Aim 2: To relate multisensory function to performance on cognitive tasks.

Rationale: Although sensory and multisensory systems undoubtedly play an integral role in creating the perceptual representations upon which cognitive processes depend, surprisingly little research has attempted to examine the relationship between (multi)sensory function and cognition. Earlier work has pointed to a striking connection between sensory function (specifically unisensory function) and cognitive abilities across lifespan, with the strength of this connection increasing with age [49-52]. Despite these findings, little subsequent work has sought to further explore this connection, and none has attempted to extend it to include multisensory abilities. In the current aim, our goal is to begin to explore the relationship between multisensory abilities and cognitive function, by using the multisensory battery described in aim 1 and relating the multisensory measures to several cognitive domains within which we have extensive experience.

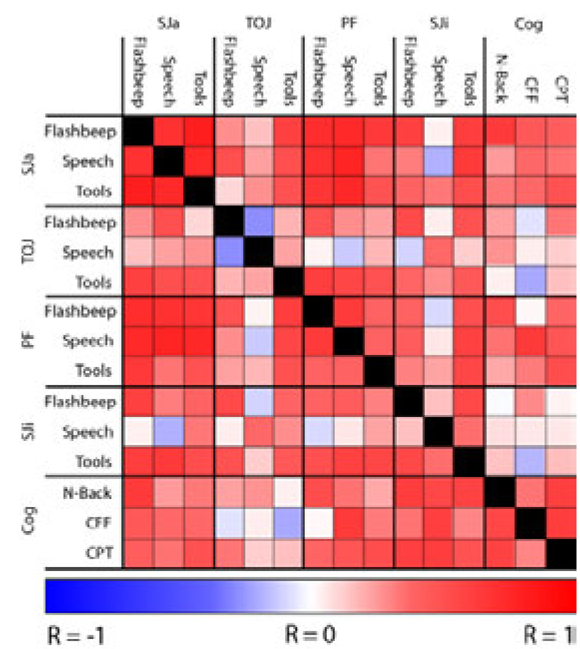

Figure 4. *Sample correlation matrix that relates across a subset of multisensory and cognitive measures. Warmer colors denote stronger positive correlations, whereas cooler colors denote stronger negative correlations.*

Participants: A subset of the individuals recruited for aim 1 will be brought back for cognitive testing. Because of practical limitations associated with using the same tests to examine cognitive function across lifespan, we will focus this preliminary analysis on younger and older adults (but see future directions).

Methods and Analyses: The cognitive battery will be made up of a series of standardized tests. In addition to compiling these scores and relating them to group (i.e., younger adult, older adult) and age, these scores will be used to create a correlational matrix similar to that shown in figure 4 and which attempts to relate the tested cognitive domains to measures of multisensory performance. For example, we may find that performance on the multisensory SJ task (i.e., width of the temporal binding window) using simple stimuli is strongly positively correlated with performance on the N-back task (see below), and less strongly correlated with performance on the Continuous Performance task, providing important insights into multisensory-cognitive links. Cognitive tasks will assess four domains of psychomotor performance and attention: vigilance, selective attention, switching attention, and divided attention. In addition, tests of working and episodic memory will also be conducted. We have had extensive experience with each of these tasks and have used them in multiple studies of cognitive aging [122-124] Test-retest reliability has been established for each of these tasks in our lab.

Attention Tasks: The Critical Flicker Fusion (CFF) task [125] will be used as a test of vigilance and measures, using ascending and descending trials from 12-50 Hz, the threshold for the perceptual transition from flashing to fusion. The Choice Reaction Time (CRT) task from the Milford Test Battery will be used to test psychomotor performance, and allows total RT to be broken down into recognition and motor components [126]. The Conners Continuous Performance Task (CPT) will be used to measure sustained attention [127]. Participants see a string of letters appearing one at a time on a computer screen. Stimuli appear for 300 ms with a response period of 2 sec for a total of 120 trials. Subjects are instructed to press a button whenever a letter appears on the computer screen and they are to not make a response when they see an A followed by an X. A version of the Posner Task [128] of attentional orienting will be used to assess the ability to disengage and shift attention to a new target. Subjects will be asked to press a button corresponding to the side of the screen on which a stimulus appears. Before the stimulus, a cue will indicate the side on which the stimulus will next appear. This cue will be valid 80% of the time. A within-modality version of a Divided Attention paradigm will require subjects to divide attention within a modality by repeating a string of digits while adding the numbers together and saying the sum after repeating the number string.

Memory Tasks: The N-Back Test will be used as a test of verbal working memory. In this task, the subject views a string of consonant letters (except L, W, and Y), one every 3 seconds. Four conditions are presented: 0-back, 1-back, 2-back and 3-back. In each of the 1-back, 2-back, and 3-back conditions, the task is to decide whether the letter currently presented matches the letter that has been presented 1, 2, or 3 back in the sequence. The Selective Reminding Task (SRT) is a multi-trial verbal list-learning task for the examination of episodic memory acquisition, encoding and retrieval [129]. This test has been widely used in studies of cognitive impairment and offers measures of storage into and retrieval from both short-term and long-term memory and intrusion errors. In addition to the measures of recall, recall failure, and consistency, we add a long-delay (20 min) recall trial and a recognition trial to assess discrimination and response bias [130]. This task has excellent predictive validity [131] and test-retest reliability [132]. A Recognition Memory Test will measure long-term episodic memory [133]. Subjects will read aloud 80 words that appear on the computer screen one at a time. After a 10-minute filled delay period, recognition memory will be tested with 80 new and 80 old words. Measures of sensitivity, bias, and reaction time can be obtained from this task, in which age differences have been well established [134].

Hypotheses and Predictions: **Our central prediction is that multisensory function and cognitive abilities will be interrelated, and that the strength of this interrelationship will increase with age.** Once multisensory systems have matured, we expect the emergence of these correlations, with the strength of some relationships being greater because of the greater dependency of the tested cognitive factor on the specific aspect of measured multisensory function (e.g., perhaps general multisensory function will map well onto memory tasks, whereas temporal multisensory function may relate more to the attentional domain). Indeed, the strength of these correlations will provide a powerful window into how specific aspects of multisensory function map onto specific cognitive abilities. In the older cohort, we expect to see increasing mappings between the multisensory and cognitive domains, as cognitive representations become increasingly dependent upon multisensory integrative capacity. The sample correlation matrix shown in figure 4 provides a bit more specificity as to some of the predicted mappings.

Limitations, Caveats and Future Directions: The cognitive measures chosen here have been selected because of their standardization and their ability to index cognitive domains that we believe are likely to be strongly tied to multisensory performance. Although it remains possible that no relationship will be found between the measured domains of multisensory and cognitive processing, the large number of tested metrics coupled with the prior work showing interactions between each (including attention and memory in the cognitive realm [53-60]) makes this possibility unlikely. One acknowledged limitation here is the lack of inclusion of children, something we hope to add in future work done in conjunction with Dr. Stephen Camarata, an expert in cognitive testing in both typically developing children and those with developmental disabilities and who is a frequent collaborator with Dr. Wallace. We also recognize that the older population may pose challenges for these tests, in part because of the enormous variance in cognitive abilities in the selected ages of our participants (66-85), and because of the well-established gender differences in cognitive aging [135, 136]. We must point out that given the focus of our work on individual differences, such variance may also represent an important strength of our proposed studies. Regardless, we believe that this work will provide an essential foundation of knowledge from which to build in future studies.

Protection of Human Subjects

Human Subjects Involvement and Characteristics, and Design

Our experiments are intended to expand scientific knowledge concerning how multisensory integration and cognitive function may be related across lifespan. As such, we will enroll participants over a wide age range spanning from 5 to 85 years. The nature of the project dictates that we will only collect psychophysical, behavioral and cognitive data from our subjects, most of which will be acquired in specific tasks that entail a response to a challenge (e.g. point to an auditory target), question (e.g., which stimulus came first, the light or the sound) or problem (e.g., 9 X 8 = ?).

Our experimental design is very simple. In aim 1 we will focus on the multisensory task battery, which can typically be completed in 2 hours (generally as two one hour sessions). In aim 2 we will focus on the cognitive battery, which will entail a series of subtests that collectively take up to approximately 2 hours to complete. In this preliminary study, we will enroll a total of 120 participants, divided into children between the ages of 5 and 85 (40), younger adults between the ages of 21-65 (40) and older adults between the ages of 66-85 (40). Due to attrition rates due to non-compliance and poor data quality in children, we have a conservative plan to recruit 20-30% above these numbers.

These experiments will include the participation of populations considered vulnerable, children and older adults. Given the lifespan focus of the proposed studies, these two groups are essential elements of our study design. Our existing protocols at Vanderbilt encompass all of the proposed testing procedures, and have been approved by the Vanderbilt University Institutional Review Board.

All data will be collected at Vanderbilt University.

Sources of Materials

Data from individuals in these proposed studies will be collected through behavioral, perceptual and cognitive measures and will be collected at Vanderbilt, and analyzed by researchers from Vanderbilt. Data will be separated from participant identifiers at collection, with code kept locked and separate from data.

Potential Risks

The proposed tasks and tests pose no risk to the health and well being of participants. Non-compliant individuals will be excused from any further testing without penalty.

Recruitment and Informed Consent

Children will be recruited through the Vanderbilt Kennedy Center (VKC) and through the Department of Hearing & Speech Sciences (DHSS), each of which has a rich history of studies on development. Dr. Wallace is a member of both the VKC and DHSS, and Dr. Newhouse is a member of the VKC. These entities each have an extensive database of typically developing children, and have multiple mechanisms in place for recruitment (e.g., website, flyers, directed mailings). Younger adults will be recruited through standard means already in place in the Wallace laboratory. Older adults will be recruited through the Center for Cognitive Medicine, directed by Dr. Newhouse, and which has an established recruitment structure targeting individuals with both healthy and pathological aging.

An informed, written consent that explains the protocol, risks, and benefits will be obtained and explained to the satisfaction and understanding of the recruit (or with children, the parent). Informed consent will be sought from the experimenter. These research studies only include participants who choose to take part, and participants are free to withdrawal at any time without penalty. Children will be given an age-appropriate description of the protocols, and the experimenter will obtain written and verbal assent, again explaining that participants can withdrawal at any time.

For the older subjects, recruitment will be carried out through newspaper advertisement and health newsletters published by our Medical Center in addition to direct mail. In our prior studies, we found that the single most effective method of subject recruitment was direct mail to randomly selected subjects from commercially purchased mailing lists. Initial telephone screening of subjects will be performed by a Recruiter/Screener. If a subject passes initial screening, he/she will be brought in for further cognitive and physical screening. Detailed medical histories will be taken and subjects will be cognitively and behaviorally screened by the psychometrist as described below. The detailed screening packet will include medical history, laboratory testing, ECG, cognitive testing, behavioral screening, and the consent form will be reviewed by the co-principal investigator (PN) prior to approval for entry into a study.

Adult subjects will consist of 80 healthy non-smoking cognitively normal adults distributed in the following age ranges: 18-40 (20); 40-65 (20); 65-85 (40), evenly divided by sex. Subjects will be matched on SES and education. All subjects will be nonsmokers and no female subjects will be currently taking hormone therapy (HT) or hormone contraceptives. If they have taken HT, or contraceptives, they must be at least one year without such treatment. Subjects will be physically healthy and have no cardiovascular disease other than mild hypertension. Subjects will also not have current Axis I or II psychiatric or cognitive disorders (see screening below).

Specific criteria for exclusion include blood pressure > 160/100 (untreated); current use of barbiturates, rifampin, insulin, carbamezepine, oral hypoglycemics, antidepressants, or lipid-lowering drugs; diabetes; untreated thyroid disease; clinical osteoporosis; severe menopausal symptoms; heavy alcohol or coffee use, significant cardiovascular disease, asthma, active peptic ulcer, hyperthyroidism, epilepsy, or current Axis I psychiatric disorders. All subjects will be taking no centrally active drugs and no drugs with cholinergic properties. A minimum of 14 days will elapse after discontinuing centrally active or psychoactive agents and the commencement of these studies.

Subjects with major concomitant illnesses will be excluded on the basis of history, physical exam, and laboratory tests assessing hematopoietic, renal, hepatic and hormonal function (CBC, complete metabolic panel, TSH, U/A, ECG). In addition, blood samples will be collected for APOE genotyping.

Cognitive and Behavioral Assessment: All adult subjects will be cognitively and behaviorally assessed by a trained psychometrist supervised by one of the PIs (Dr. Newhouse) to exclude individuals with evidence of cognitive impairment. Overall intelligence and IQ will be estimated using the Wechsler Abbreviated Scale of Intelligence (WASI)[1]. This test was developed specifically for estimating premorbid intellectual functioning in adults and was developed and co-normed with the Wechsler Adult Intelligence Scale-III (WAIS-III). Subjects will also be evaluated using the Mini Mental State Exam (MMSE)[2], Brief Cognitive Rating Scale[3], and the Mattis Dementia Rating Scale[4] to establish a Global Deterioration Scale score (GDS) which rates the degree of cognitive impairment[5]. Subjects will be required to have a GDS score of 1-2 and a MMSE score of greater than or equal to 27. Subjects will be excluded if they score below 123 on the Mattis scale and will also be matched as closely as possible in terms of educational background.

As an index of subjective cognitive status, subjects will the Memory Functioning Questionnaire[6], Memory Self-Rating Questionnaire[7], the Neurobehavioral Function and Activities of Daily Living Rating Scale[8], the Informant Questionnaire on Cognitive Decline in the Elderly[9], the four cognitive items from the Geriatric Depression Scale[10], 10 cognitive items from a telephone-based screening for MCI, and 23 items from the Memory Assessment Questionnaire adapted in part from the Functional Activities Questionnaire[11]. A Cognitive Complaint Index (CCI) will be calculated as the percentage of all items endorsed.

Behavioral screening will consist of a partial Structured Clinical Interview for DSM-IV-TR (SCID)[12] to establish the presence/absence of Axis I psychiatric disorders. In addition, subjects will be evaluated with the Hamilton Depression Scale (HAM-D)[13] and will complete the Beck Depression Rating Scale (BDI)[14] and the Hamilton Anxiety Inventory[15]. A cut off score of 7 will be used for the BDI and 8 for the HAM-D. Subjects scoring above these values will be excluded. Information obtained from the SCID may be used as potential covariates in data analysis.

Protections Against Risk

The risk to participants is minimal, carrying no significant health risk, and undue complications are not anticipated. All participants' data will be coded at the time of collection, and participant codes will be kept separate from data.

Potential Benefits of the Proposed Research to Human Subjects and Others

The participants will be told that, although they might not benefit directly from this research, society may benefit from the knowledge gained from these studies. Participants will also receive compensation for their time in the form of money, gift cards, or class credit.

Importance of the Knowledge to be Gained

The data generated from this project will have a number of possible important benefits. It will contribute to the knowledge of multisensory integration in general, and will represent the first effort to examine how multisensory processes change across lifespan. In addition to the relevance of this work for charting the chronology of normal multisensory development, the work is of clinical relevance because of the wide range of developmental disabilities in which there are sensory impairments, including, but not limited to, autism, schizophrenia, and dyslexia. In addition, we argue that multisensory function is a foundation for cognitive function, and that changes (and individual differences) in multisensory abilities will be related to changes (and differences) in cognitive function. Such a framework is extremely important given the central importance of cognitive capacity in underlying our ability to function in real-world settings, and in the changes that occur in cognition as part of the normal aging process. Since the risk to the participants is negligible, these benefits justify any potential risk.

Inclusion of Women and Minorities

We will make every effort possible to achieve a racial/ethnic distribution of participants that is representative of the greater Nashville population, and the county as a whole. Given the diverse population of Nashville, and of Vanderbilt University, we are confident in our ability to recruit a representative sample. We will target race and ethnicity in proportion to the general population. Based on recent demographic information, the approximate racial composition of Nashville and the Middle Tennessee metropolitan area is 61% white, 28% African-American, 10% Hispanic and 1-2% from other racial groups. Our targeted enrollment table reflects these distributions.

Targeted/Planned Enrollment Table

See link below for updated notice:
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-086.html

Inclusion of Children

Given that a component of this research focuses on detailing the development of multisensory processes, these studies will include children. The plan will include children between the ages of 5-21, given the gap in our knowledge concerning multisensory processing at these ages. Our research group has extensive experience working with children at these age ranges (both typically developing along with those with developmental disabilities). Our lab space in the Bill Wilkerson Center is designed specifically for experiments with children. Recruitment will take place in conjunction with the Vanderbilt Kennedy Center and the Department of Hearing & Speech Sciences at Vanderbilt, both of which have extensive databases of children interested in taking part in research. Given the psychophysical nature of the tasks that we employ (many of which are similar to video games), we expect the children to readily complete all of the proposed tasks.

Multiple PI Plan

Wallace and Newhouse will serve as multiple PIs for this R21 application. Wallace will serve as the contact PI. As detailed in the accompanying application and biographical materials, the two PIs have complementary interests that add tremendous strength and expertise to the proposal. Wallace brings tremendous experience in studies of multisensory processes. Although initially founded in neurophysiological studies of multisensory encoding, his laboratory has now expanded to include studies grounded in psychophysical approaches. These studies are largely oriented toward detailing how multisensory stimulus combinations impact behavior and perception, the cornerstone of the current proposal. In addition, there is a large emphasis in the Wallace laboratory in detailing the developmental antecedents leading up to mature multisensory representations. Newhouse brings tremendous experience from the perspectives of cognition and cognitive aging, and he also brings a great wealth of knowledge concerning psychopharmacological approaches toward studying cognition and aging. Collectively, given the emphasis of the work on multisensory and cognitive processes, as well as examining these issues across lifespan, it will be of great benefit to have both Wallace and Newhouse serve as PIs.

A dual PI structure with these two individuals is ideal for a number of reasons. First, as outlined above, each brings a wealth of experience and differing perspectives to this role. Second, the differing emphases of the two aims makes the dual structure logical, particularly given the natural division of responsibilities outlined below. Finally, Wallace and Newhouse have already developed a strong working relationship since the recent arrival of Dr. Newhouse. The proposal detailed here is a natural extension of their discussions of areas of common interest.

In regards to the division of responsibilities, Wallace will oversee the experiments detailed in aim 1 and that seek to chart changes in multisensory processing across lifespan. He is well qualified for this work not only because of his lab's strong focus on multisensory psychophysical research, but also because of his prior and ongoing work on developing and aging populations. Newhouse will oversee the cognitive studies that form the focus of aim 2, given his extensive experience in administering and interpreting cognitive tests in younger and older adults.

We are highly comfortable with this natural division of labor. In the unlikely event of a disagreement among the PIs, a committee appointed by the Vanderbilt Brain Institute will serve as arbiter.

Resource Sharing Plan(s)

The unique research resources that stem from the projects outlined in this proposal are in both the analytical and conceptual realms. These include the development of the psychophysical battery needed to characterize multisensory processes across lifespan, the development of the correlational analyses across the multisensory and cognitive domains, and the knowledge set gained concerning changes in multisensory abilities across lifespan and its relationship to higher cognition. These tools and the associated data are currently under development and refinement in our laboratories, and will be provided to NIH upon request. We have no proprietary interest in these tools, and are developing them so that they can be made available to and utilized by the broad research community interested in similar issues. As such, we envision this analysis suite (which is largely developed in the MATLAB programming environment) as being an important means to enhance the value of this NIH-sponsored research. In addition to sharing these unique research resources with the research community, we will also provide copies of documents or samples of any materials developed under this NIH grant award. In summary, any and all resources developed during this NIH-funded project will be made readily available for research purposes to qualified individuals within the scientific community.