

**UNIVERSITY OF WATERLOO**

**INFORMATION CONSENT LETTER**

**Structural and functional correlates of audiovisual integration**

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**INTRODUCTION**

You are being invited to take part in a research study. Before agreeing to participate in this study, it is important that you read the study procedures. The following information describes the purpose, procedures, benefits, discomforts, risks, and precautions associated with this study. It also describes your right to refuse to participate or withdraw from the study at any time. In order to decide whether you wish to participate in this research study, you should be aware of its risks and benefits to be able to make an informed decision. This is known as the informed consent process. Please ask the study staff to explain any words that you do not understand before signing the written consent form during in person visit. Make sure all your questions have been answered to your satisfaction before signing this form.

**PURPOSE**

Auditory and visual information about an audio-visual event can arrive at the brain at different times. In order to represent audiovisual events as truly simultaneous, the central nervous system must combine audiovisual information that co-occurs within a small period of time, referred to as the ‘temporal binding window' (TBW). Work in our lab has shown that in older adults, the TBW broadens leading to impaired audiovisual integration (i.e., older adults bind audiovisual information across a wider span of time). Due to this, older adults experience behavioral deficits include difficulty in carrying out daily living tasks, such as driving which requires significant amount of multisensory integration. Older adults are also more susceptible to risk of falls and errors in understanding speech due to this deficit. Although, research has been conducted to investigate change of the TBW with age, the neural mechanisms that subserve these changes of the TBW during older aging are yet to be determined. Transcranial magnetic stimulation (TMS) is a non-invasive techniques which can be used to investigate cortical excitatory and inhibitory (neural) mechanisms1. TMS produces magnetic waves which generate electrical activity in a local population of neurons. Varying the intensity of the stimulation can help to investigate the state of excitability of the neural circuit. Alterations in human cortical excitability have been shown in neurological disorders like stroke, epilepsy, dementia and movement disorders like Parkinson’s and dystonia disorders2. Finally, recent work has suggested that tDCS can reduce the width of the TBW in younger adults18. Measuring changes in GABAergic activity in young versus older adults could provide insight into whether decreased levels of GABA in older adults are related to impaired sensory integration such as the width of the TBW.

The purpose of the present work is to provide a more detailed understanding of the brain mechanisms of how audiovisual integration changes with age which may help to understand possible treatment options.

**PROCEDURES**

**Time commitment**

If you agree to participate, all assessments will be first be performed in one (TMS session) which involves us collecting some brain stimulation measures using transcranial magnetic stimulation. This session will take approximately 3.5 hrs of your time. You will be remunerated $35 at the end of the session. The study is being performed at the he Sensorimotor integration and neuroplasticity lab (SNIP) (AHS building, room 2694) in the Department of Kinesiology at the University of Waterloo.

**Procedure**

Two Main task will be performed, measurement of behaviour tests and non-invasive brain imaging will be done using transcranial magnetic stimulation (TMS).

Behavioural Measures

To screen for normal vision, we will record the best corrected visual acuity (BCVA) and contrast sensitivity. BCVA will be recorded uniocularly and binocularly under standard testing conditions22. Visual acuity and contrast sensitivity testing will be performed using the Freiberg visual acuity test23, an automated procedure for the measurement of visual acuity. Landolt-C optotypes will be presented on a monitor in one of eight directional orientations. Participants will be asked to respond to the orientation of the Landolt-Cs using a keypad**.** Auditory thresholds will be determined using a smart phone application ‘UHear. UHear is an application to test hearing loss. It was developed by a Canadian based hearing aid company ‘Unitron’. It functions on IOS devices like ipad an iphone and is available for free download in the apple store. The application is self administered and user friendly. The program uses automated audiology to test hearing.

TOJ and SJ task:

Two Behavioral measures of audiovisual integration will be measured to quantify the TBW. The first task will be the audiovisual simultaneity judgment task (SJ). In this task, you will be asked to indicate whether a single auditory beep (1850Hz, 7ms duration) and a white circle (1cm diameter, 17ms duration) occurred at the same time or not and which one occurred first.

**Brain stimulation measures (TMS session)**

We will use two different non-invasive techniques.

**Phosphene protocol:**

**Phosphene hotspot and phosphene thresholds**

Phosphene thresholds will be measured using the same MagStim Bistim magnetic stimulator connected to a figure-of-eight coil to deliver ppTMS. The coil is held tangentially to the scalp, handle posterior, approx. 90 degrees to the midsagittal line. The optimal occipital stimulation site will be determined using a 3×3 cm grid. The center of the grid is located 1.5 cm lateral and 3 cm dorsal of the inion. To find phosphene hotspot, each point on the grid will be stimulated three times at 60% of maximum stimulator output and the participant asked to verbally report if they saw a dot/flash of light. If phosphenes in the contralateral visual field are not reported at any of the nine grid points, the TMS intensity will be increased by 10% and each point on the grid will be stimulated again. The process will be repeated until the participant reports seeing phosphenes or stimulus intensity would exceed 100% of maximum stimulator output. Participants who do not report seeing any phosphenes before 100% of maximum stimulator output is exceeded will be excluded from the study. If you perceive phosphenes, the grid location that elicits the most reliable phosphene will be used for the remainder of the session (“hotspot”). Resting phosphene threshold will be determined at the hotspot by starting at the intensity at which phosphenes were first noticed and decreasing the stimulator output in increments of 2% until phosphene probability fell below 5 out of 10 trials and then incrementing stimulator output by 1% until the 5 out 10 threshold s reached or exceeded.



Image extracted from Khammash et al(D Khammash et al., 2019)

**SICI and LICI**

Threshold tracking (TT) technique will be used to quantify the extent of inhibition and disinhibition in the visual cortex. We will use different test and conditioning intensities over the visual cortex to produce phosphenes.

After delivering the magnetic pulse, we will ask you about any perception of visual disturbances or grating like stimuli that you may notice in your right and lower side of the visual field. You will be requested to use a mouse to draw the shape of the perceived phosphene on a computer screen in a darkened room. The size of the phosphene may vary throughout the experiment. Some people may not be able to see any such disturbances in perception. If you experience this, please let us know.

As a participant in this study, you will be asked to sit comfortably with your head supported by a chin rest while measures of cortical excitability are being recorded. These measures will utilize paired pulse TMS as described above to evoke muscle activity. Throughout the study, muscle activity will be measured using EMG as described above.

If you do not perceive phosphenes after administration of the phosphene protocol, you will be ineligible for this particular part of the study. Your data will be analyzed as follows:

-Any data collected prior to the phosphene protocol ( motor cortex threshold, behavioral TOJ and SJ experiments) will be included in the analysis and further publications

-Any data that directly relates to the phosphene protocol will not be included for any further analysis

Motor Thresholds

This method involves two techniques. The first technique is electromyography (EMG). EMG involves attaching electrodes to the skin overlying muscles of the index finger to record muscular activity. A total of 2 electrodes over the first dorsal interosseous (FDI) muscle located on the index finger are to be placed, and a 3rd electrode is to be placed on the ulnar styloid process at the wrist to function as a ground electrode. You will be asked to help place these EMG electrodes on the skin of your right hand, to minimize the amount of time a study team member is closer than 2m. You place the electrodes under the instruction and observation of the study team while they maintain 2m. If you do not feel comfortable placing the electrodes, you may ask the study team for help in putting the electrodes on. If you ask the study team for help, the study team member will wear a medical-grade face mask, full face shield and sanitize their hands before placing the electrodes on your hand. In some cases, the quality of the information coming from the electrodes that you have placed may not be good enough. In these cases, a study team member may ask permission to replace some electrodes. The study team member who replaces the electrodes will wear a medical-grade face mask, full face shield and sanitize their hands before replacing the electrodes. EMG electrodes are disposable and are held in place with a mild adhesive after cleaning the skin with alcohol and a mildly abrasive skin preparation lotion (NuPrep or Lemon Prep). The second method is TMS which is used to briefly stimulate specific areas of the brain either during or before you perform specific sensorimotor tasks (procedures are described below). We will use brain-sight software to first locate and monitor the specific brain region that is to be stimulated. For this, we will use a washable marker and draw a dot on your forehead, nasal bridge, and earlobes. During the experiment, we may need to calibrate the head location again using these marked dots. An infrared pointer will be sanitized and used to be touch the bridge of the nose, tragus of each ear and outer canthus of each eye. **During this process, the researcher is less than one meters of distance from the participant. This process will take approximately 1 minute. All through the process, the researcher (medical grade mask and face shield) and the participant(medical grade mask) will continue to wear PPE.** Following localisation, we will set up the TMS instrument. TMS involves delivering brief magnetic pulses over specific locations on your head. You will be asked to keep your head as still as possible. To assist with this your head will rest against a padded support. TMS uses a magnetic stimulator that consists of a set of electrical capacitors that can store and rapidly discharge electricity into a coil of electrical wires that are encased in plastic. The plastic case rests against your head. As electrical current flows through the coil, a magnetic field is generated that penetrates the skull and induces a second electrical flow of current in the brain. This procedure is not painful, and the potential risks are outlined below (see risks section). Normally you will hear a clicking noise as the current flows through the coil however, you will be provided with earplugs for hearing protection. You may experience involuntary activation of different muscle groups of the forearm and/or hand depending on the position of the coil over the head. These muscle contractions are mild and should not provide any discomfort. The study team member will be required to hold the coil on top of your head and make moment-to-moment adjustments in the position of the device. During this time, the study team member will wear a medical-grade face mask and full-face shield. All TMS procedures will be performed at the University of Waterloo (200 University Ave West, Waterloo) and will be delivered using a Magventure stimulator (Model: MagPro R30, Magventure, [www.magventure.com](http://www.magventure.com)).

TMS will be used in the study to induce brief and transient excitation in a specific region of the brain. TMS activates interneurons in the brain that then will activate larger projection neurons. For instance, if the stimulation is applied to the motor cortex of the brain, the neural pathway to a specific muscle will be activated. Interneurons are either inhibitory or excitatory, meaning they either somewhat block or promote output from a given brain area depending on how the stimulation is applied. A “brief and transient excitation” then means that the stimulation will activate excitatory interneurons that will somewhat increase the output from the brain area over which it will be applied. This will last for only a brief time (i.e. on the order of milliseconds to a few minutes) before the neurons return to their baseline state. For the purposes of this study, TMS will be applied with a single magnetic coil either as single pulses or in pairs of two pulses. For TMS measures, active (AMT) and resting motor thresholds (RMT) will be determined.

**INCLUSION CRITERIA**

For screening purposes, to participate in this study you must be 18 years to 80 years old must have normal or corrected to normal vision (using spectacle/contact lenses) and normal hearing. You will not be able to participate in this study if you use hearing aids. You may also not be able to participate in this study if you have any known auditory or visual deficits. You must also have the ability to acknowledge instructions and provide informed consent. Participants are required to be right-hand dominant to reduce the variability in measure of brain stimulation that is being recorded for this study.

**Online screening**

To determine eligibility prior to the in-lab session we will ensure that all the participants receive the study materials prior to the study visit. If you agree to participate, the researcher investigators will set up a skype/zoom/Teams meeting to explain the study procedures in depth, review eligibility, inform about any specific things that are excluded or you need to avoid (e.g: participants should sleep adequately, cannot have excessive alcohol, and have a good meal before the study session) and answer any questions that you may have. Please make sure to read the questions thoroughly. If you answer ‘Yes’ to any of the questions on the screening form, you may not be able to participate due to the study eligibility. University of Waterloo researchers will not collect or use internet protocol (IP) addresses or other information which could link your participation to your computer or electronic device without first  informing you. If you have limited access to the internet or do not wish to meet online, please contact one of the researchers so you can participate using an alternative method such as telephone call.

**Exclusion Criteria:** In order to participate in this study, you must not have (and have no history of being treated) for a major neurological illness or event such as stroke, epilepsy, or peripheral neuropathy. In addition, you must have no known allergy to rubbing alcohol, gels, or adhesives. You must be fluent in English enough to understand instruction solely in English. You will be excluded from the TMS portion of the study if you have metal or magnetized objects in your body. Examples of these metal objects are cardiac pacemakers, surgical clips (e.g., aneurysm clips in your head), artificial heart valves, electronic ear implants, metal fragments in your eyes, electronic stimulators, and implanted pumps or pregnant. A detailed inclusion/exclusion will be determined and documented using a clinical information form and TMS screening form after you arrive to the lab.

**BENEFITS**

There is no known direct benefit, however, by participating in this study, you will benefit by furthering your knowledge of experimental procedures commonly used in neuroscience research. Your help will contribute to our knowledge about how multisensory integration declines with age and decline in perceptual deficits can be linked with structural changes in the brain. This study may also help to understand possible treatment options in this population.

**Risks:**

There is minimal risk posed by the use of any of the techniques. For behavioral experiment in session three in which we plan to use artificially blurred vision using trail lenses placed on a trial frame, some participants may be feel discomfort and headache. You can remove the trail frame and request to take breaks if you experience any discomfort. For brain stimulation, all EMG electrodes are surface electrodes and do not actually contact the skin. A conductive gel provides the contact between the skin and the recording electrodes. In rare instances it is possible that your skin may be sensitive to the conductive gels or rubbing alcohol used for surface recordings. In such cases a skin rash is possible. Using TMS we will deliver very brief electrical stimulation to activate nerves in your arms or legs which can cause a mild tingling sensation. TMS has been used in a growing number of laboratories worldwide since 1985. TMS is a widely used technique that excites brain tissue in humans for both experimental and clinical purposes. The risks for this study are minimal, however, a series of adverse effects that can be induced by TMS have been identified. There is no evidence that the procedure is harmful if appropriate guidelines are followed345.

*The following are* ***risks and discomforts*** *that are possible when undergoing TMS:*

* 1. The procedure is painless, although it can cause muscles to contract immediately following stimulation, which may lead to residual soreness, caused by muscle fatigue, over the duration of the experiment.
	2. Approximately 1 in every 10 participants undergoing TMS experience headaches or dizziness, which are believed to be due to excessive muscle tension. Acetaminophen promptly resolves the discomfort in most cases. In the event Acetaminophen does not resolve discomfort participants are directed to Health Services if a UW student / employee, or to a walk-in clinic or family doctor appointment.
	3. Approximately 1 in every 100 participants undergoing TMS experiences neck stiffness and pain. This is believed to be due to the straight posture of the head and neck during the application of TMS. Acetaminophen promptly resolves the discomfort in most cases. The researcher should be advised at the first opportunity when the participant begins to experience neck stiffness or pain. The participant may choose to withdraw or to rest and change posture for several minutes before resuming the procedures. If neck stiffness and pain persist and in the event Acetaminophen does not resolve discomfort participants will be directed to Health Services if a UW student / employee, or to a walk-in clinic or family doctor appointment.
	4. TMS produces a loud clicking noise when the current passes through the coil. This loud click can result in tinnitus (i.e., “ringing” in the ears) and transient decreased hearing if no ear protection is used. Animal and human studies have shown that earplugs can effectively prevent the risk of hearing disturbances. In the current study participants will wear earplugs for hearing protection.
	5. The use of single paired pulse or very low frequency (repetitive) TMS has never induced a seizure in a healthy participant. However, there is the possibility that TMS can induce a convulsion even in the absence of brain lesions, epilepsy or other risk factors for seizures. Only 7 cases of convulsions have been reported using single pulse TMS in patients with pre-existing brain damage despite extensive use in both the healthy and patient population. The overall risk for seizures during TMS is thought to be in the order of 1 in 1000 studies. In the event that convulsions do occur they can result in longer-term quality of life changes, including suspension of driver’s license until it has been confirmed that the convulsions will not re-occur. However, the forms of magnetic stimulation (i.e. single pulse, paired-pulse & low-frequency, < 1 Hz, repetitive) used during this study have never been reported to induce a seizure and are well within the limits recommended by the guidelines5.

**Remuneration**

You will be remunerated $35 at the end of the study session. The amount received is taxable. It is your responsibility to report this amount for income tax purposes.

**Participation in the experiment:** You may decide not to partake in this research or not to answer individual questions. However, some of the questions regarding your health are being asked to reduce the risks associated with TMS. You may not be able to participate if you do not want to answer the questions that are directly linked to the identified study risks. Withdrawal from the study may occur at any time by informing the experimenter that you would like the experiment to stop. The test will also be terminated if the experimenter detects any signs of discomfort or distress. Any data or information obtained before the time of withdrawal will not be used for further analysis without your consent. You may request your data be removed from the study after study completion up until 12 months. However, data cannot be withdrawn once papers and publications have been submitted to publishers. Partial remuneration will occur if the experiment stops early and the participant have spent at least 30 minutes of time doing the experiment.

**Questionnaires:** Participants will be asked to fill out screening forms for the TMS testing that indicate all of the exclusion criteria.

**CONFIDENTIALITY AND SECURITY OF DATA**

Your identity will be kept confidential and will not be passed to a third party. Only the researchers associated with the study (Dr. Michael Barnett-Cowan and Viquar Unnisa begum) and the research assistants will have access to the data. The collected data will be coded with participant numbers (not names). Paper data will be kept in a locked area (CCCARE) for 7 years then shredded and electronic data will be kept on a password-protected computer (CCCARE) for indefinitely after publication.

**QUESTIONS**

Any questions with regard to this research should be directed to Dr. Michael Barnett-Cowan, 519-888-4567 Ext. 39177.

**ETHICS CLEARANCE**

This study has been reviewed and received ethics clearance through a University of Waterloo Research Ethics Committee (ORE#23241). If you have questions for the Committee contact the Office of Research Ethics, at 1-519-888-4567 ext. 36005 or ore-ceo@uwaterloo.ca. “

References:

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3. Huang, Y.-Z., Edwards, M. J., Rounis, E., Bhatia, K. P. & Rothwell, J. C. Theta burst stimulation of the human motor cortex. *Neuron* **45,** 201–6 (2005).

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**UNIVERSITY OF WATERLOO**

**Ms. Viquar Unnisa Begum and Dr. M. Barnett-Cowan**

**CONSENT FORM**

Structural and functional correlates of audiovisual integration

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Have been informed and I am aware of the aim of this study, and have read the information consent letter and the clinical information form. I acknowledge that I am under no obligation to take part and may withdraw from the study at any time during the experiment. If wish to have my data destroyed and excluded from the study, it is my responsibility to inform the researcher of my request.

I am aware that the researchers will be asking me questions concerning my health. This information will remain confidential and I will be free to refuse to reply to any question that I am unwilling to answer.

I acknowledge that I am free to ask questions and to withdraw from this study at any time. I also acknowledge that if I feel uncomfortable, I may ask the researcher to stop it immediately.

\_\_\_\_ I agree to take part in the study. I will receive a copy of the information consent letter and signed consent form.

\_\_\_\_ I have participated in this study and would like to receive a summary of the results when the study is completed.

In no way does signing this consent form waive your legal rights, nor does it relieve the investigators or involved institution from their legal and professional responsibilities.

**PARTICIPANT**

NAME \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

SIGNATURE\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date \_\_\_\_\_\_\_\_\_\_\_\_

**INDIVIDUAL OBTAINING CONSENT**

NAME \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

SIGNATURE\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date \_\_\_\_\_\_\_\_\_\_\_\_