**PROTECTION OF HUMAN SUBJECTS**

**Risks to Human Subjects**

1. Human subjects involvement and characteristics

**Inclusion Criteria**

One sample of healthy participants, ages 13 - 20, will be involved in the proposed investigations. All participants will have normal or corrected-to-normal visual acuity of 20/20, will be free of color-blindness, and will be free of psychological, neurological, and developmental disorders. Participants under the age of 18 must have a parent or legal guardian present and both parties must assent and consent to study procedures, respectively.

**Exclusion criteria**

Participants will be excluded from taking part in our studies if:

1. They have any MRI contraindications. This includes: dental braces, hair weaves that use wire, pacemakers, and implanted medication pumps, metal plates in the skull, or metal objects inside the body.
2. They are pregnant because the effects of MRI on fetuses are still unknown. Pregnancy will be ascertained by self-report and/or pregnancy test. Female participants will be given the option of leaving the experiment after viewing the results of their confidential pregnancy test.
3. They are very claustrophobic. Since MRI experiments involve being in a very small, enclosed space for a long period of time, claustrophobic participants are not allowed to participate in the experiment. Participants are also asked to report any medications they are currently taking. Medications may alter neurotransmitter levels throughout the brain, potentially altering neural function and cognition.
4. They suffer from intellectual retardation (IQ<70), neurological disorders including epilepsy, brain tumors, substance abuse disorders (within 6 months of screening interview), and/or stroke. We will exclude participants who self-report head trauma. Head trauma can cause mild to severe alterations in cognitive function, as well as changes in brain function and white matter connectivity.
5. They fall outside of our age range.
6. They do not meet the cut-offs of various standardized tests that will be administered.
7. If they move excessively in the mock scanner or in the real scanner. We will quantify head motion as the mean relative frame wise displacement by using the Framewise Integrated Real-time MRI Monitoring software that provides the scanner operator with head motion analytics in real-time. We will exclude subjects who are at least 2 standard deviations above the mean.

To retain participant privacy, answers to all questions are voluntary. Also, participants are permitted to exit the experiment without apparent reason after having been asked these questions.

1. Research materials

Demographic information will be collected from all participants.

Participant identification numbers will be coded using a systematic and arbitrary database number. Personal identifying information will not be available from the data collected. All paper forms will be kept in a locked filing cabinet in the sponsor’s laboratory. All digital data, including imaging data, will be kept on password-protected computers. Digital data also will be backed up to external hard drives, and these backup media will be stored in a locked cabinet in the sponsor’s laboratory. Only the PI, sponsors, and study personnel will have access to the data. All paper and digital data will be de-identified and labeled with ID numbers. The key linking ID numbers with identifiers (name and contact information) will be kept separately from participants’ data, with access restricted only to the PI and research staff.

1. Potential Risks

There is minimal risk to subjects in our experiments. Risks to confidentiality are negligible because (a) participants will be identified by numbers, not name, in data files; (b) data will be kept locked in the PI’s lab; and (c) will not gather any detailed health information. All information regarding the participants’ demographics, performance in experiments, and neurological history will be kept private and confidential.

*Behavioral Tasks*

The risks in behavioral aspects of this research are minimal and do not constitute long-range risks to the subjects. As with most psychology experiments, there is the risk of boredom, mental fatigue, or frustration with performance. Tasks are described in detail in Approach.

*Imaging using MRI*

All participants are screened to exclude those with metallic implants. Aside from this, MRI poses no known physical risks. One cannot, however, be certain that long-term hazards of MRI are nonexistent, since this technique only has been in clinical use for approximately 25 years. There are also several short-term risks:

* *External projectile risk*: The size and strength of the MRI magnet is such that it can attract very heavy iron-containing objects (e.g. oxygen tanks). This can cause serious injury and even death, although death due to such incidents is very rare. Smaller objects, including bobby pins and nail clippers, also can cause serious injury to patients in the scanner.
* *Internal projectile risk*: Metal that is embedded in bodily tissue, such as a metal plate or an implanted medical device (e.g. pacemaker), can move, rotate, or be extruded from the body if placed proximal to a strong magnetic field. Swelling and irritation of the skin due to motion of iron oxides in tattoo pigments is also possible.
* *Burn risk*: There is a risk of burns from medicinal patches during MRI. Such burn risks also are associated with ECG leads, presence of piercings, or any metal cabling.
* *Acoustic risk*: The sound level of a typical MRI scanner during an imaging sequence is approximately 95 dB, which is higher than OSHA guidelines. This could cause damage to the ears after prolonged exposure. Participants will wear high quality hearing protection while in the scanner.
* *Gradient field change*: The changes in gradient fields used to acquire MRI images can cause peripheral nerve stimulation effects that range from distracting to painful.

In addition to these physical risks, there are also minimal psychological risks due to MRI scanning, which include:

* *Risk of incidental findings*: There is the risk of an incidental abnormal finding in an MRI image, which could be distressing to the participant. In the case of an incidental finding, we have an incidental finding procedure (described below).
* *Risk of anxiety*: There is some risk of anxiety about the scanning environment. Remaining still in an enclosed space may cause some discomfort or anxiety for participants.

**Adequacy of Protection against Risks**

1. Recruitment and informed consent.

Healthy individuals will be recruited through physical flyers posted around the greater Philadelphia area (see Facilities and Other Resources), online ads (via Facebook, Craigslist, etc.), in coordination with participating schools, youth organizations, and clinics, as well as databases of participants that had consented to being contacted for future research opportunities. A brief description of the study, including our target age ranges, will accompany all advertisements. Participants or guardians will receive an explanation of the research over the phone, via email or in person. If they are still interested in participating, a phone screen will be conducted. If a participant is under the age of 18, a parent or legal guardian must be present during the screening procedure. Both parents and participants will be required to provide verbal assent and consent prior to reviewing screening criteria. Participants will be assured that they are free to not answer any questions that they find uncomfortable. Ineligible participants will be informed of their ineligibility but will not be told why they are ineligible. This will maintain integrity in screening procedures by keeping exclusion criteria private.

Eligible participants still interested in participating will be scheduled for a visit. Documentation of the screening procedure will be stored electronically for each participant. All participants will have the nature and goals of the research explained to them. All participants will understand that they may withdraw from the study at any time without penalty. All participants who are suitable and agree to enroll in the study will have the procedures explained in full. We will obtain signed consent from all participants.

The research protocol and consent form will be approved by the Institutional Review Board (IRB) of Temple University. Consent is documented by saving all signed consent forms and by checking a box on a separate sheet that lists standard experimental procedures. In compliance with the NIH data sharing initiative, imaging data without any personal information attached may be shared with other investigators or public data repositories. This provides the research community with open access to datasets contributed by labs around the world. Any data that is shared will be completely anonymized with only demographic information about age, gender, handedness, and group membership provided.

1. Behavioral Tasks

Though study tasks demand sustained attention for extended periods of time, they have also been designed to be engaging to capture participants’ attention. Video stimuli of similar lengths have been successfully used with developmental populations in the past (e.g., Karim & Perlman, 2017). To protect against fatigue, participants will be given a short (1-2 minute) rest periods between fMRI scans if requested, and will be able to discontinue testing at any time. Should participants appear to be anxious and frustrated about the tasks, testing will be terminated. Participants will be told that they are free to withdraw from the testing at any time.

1. Imaging using MRI

Participants with claustrophobia or lower level discomfort due to the enclosed nature of the scanner will be excluded from participation. Anxiety will be minimized by explaining the scanning procedures and the nature of the MR scanner in detail to participants prior to enrollment in the study, and through practice in the mock scanner. During the scan, participants are continuously monitored visually and through an intercom system for any potential problems, and participants are assured that they can and will be removed from the scanner at any time if problems arise or if participants indicate that they are experiencing any discomfort.

We will minimize physical risk in the following ways:

* *Minimizing external projectile risk*: To protect against external projectile accidents, participants are required to remove all metal objects, including clothing with metal fasteners, jewelry, and bobby pins. A wand metal detector will then be used to further ensure that no ferrous metal is present. Other personnel are restricted from areas near the magnet to help ensure that no iron-containing materials are inadvertently brought in the MRI room. The MRI scanner is operated by trained technicians who are trained in MRI safety issues.
* *Minimizing internal projectile risk*: Participants with embedded metal will be excluded from participation.
* *Minimizing burn risk*: Participants will be required to remove any medicinal patches and all metal objects prior to the scan.
* *Minimizing acoustic risk*: Participants will be required to wear earplugs, which reduce the sound level of the scanner to approximately 14-29 dB. This is within the range of OSHA guidelines.
* *Risk of gradient field change*: Participants will be asked and reminded not to cross their arms or legs during the scan.

If an abnormality is detected during the course of scanning or analysis, I will follow the standard protocol outlined by TUBRIC and refer the scan in question to experts in neuroanatomy on the TUBRIC staff. They will examine the scan and, if they also suspects that there is an abnormality, they will refer the de-identified scan to a consulting radiologist or neurologist at Temple University, University of Pennsylvania, or Jefferson Hospital, or their affiliate hospitals. If the diagnostician feels that the scan was misread, no further action will be taken. However, if he or she agrees that additional action should be taken, the sponsor will make initial contact with the participant, either by telephone or in person (not by email which should be regarded as public) regarding an anomalous MR image. The discussion will be restricted to these points:

* Something unusual was identified.
* It may or may not be of clinical significance.
* We recommend he/she obtain clinical advice.

We will make the images we collected available to the participant. However, it should be remembered that we don't collect diagnostically useful images and participants will be informed of this.

D. Collection of Questionnaire Data. Questionnaire data will be recorded digitally and secured via encryption. Participants will be afforded adequate privacy, such that questionnaire data will not be accessible to guardians. Deidentified data from questionnaires will be made publicly accessible following the study’s conclusion. Guardians will not be privy to a participant’s internal identification number, which will limit the possibility that the responses could be connected to individuals following public release.

Minimizing risk of coercion. Coercion is a common problem in all research involving human subjects. The risk of coercion will be minimized by following standard procedures for obtaining informed consent. For all participants under the age of 18, we will obtain signed informed assent, and signed informed consent from the participants’ parent or legal guardian. Both parties must agree to participation for the participant to be enrolled. We will fully explain the study procedures, risks, benefits, and alternatives to all participants. Participants will be free to withdraw at any time, and will receive compensation for time devoted to the project. Comfort with study procedures will be assessed several times during study participation, which will allow participants to end study procedures, if they so choose.

Compensation. Participants will be paid at a rate of $20/hr for completing the study. This is consistent with payment for similar fMRI studies within Dr. Helion’s lab. This rate of compensation is commensurate with standard rates paid for developmental research at Temple University and not considered unduly coercive. Compensation for enrollment will be given directly to the participant, or to the parent or guardian with the participant’s permission, in the form of gift cards. Additional compensation may be provided to guardians who transport or accompany their children at a rate to reduce financial logistic burden.

D.3.8 Additional protections for children. Although the proposed research involves no greater than minimal risk, any form of research with children requires careful attention to issues of protection and tolerability. A series of procedures therefore will be used to minimize risk for distress in the younger children and adolescents who participate in the proposed research. Although our assessments do not directly gauge maltreatment, research staff still will be vigilant towards any signs of child maltreatment or neglect, which will be reported to Child Protective Services. All research staff will complete Pennsylvania State’s Mandated Reporter Training. If, during assessment procedures, clinical or research staff identifies a condition that should require immediate clinical intervention or official reporting, all necessary steps will be taken. If the staff member believes that the child is at significant risk, or poses significant self or other-destructive behavior, the applicant and the sponsor (Dr. Helion) will be notified immediately and a clinically trained consultant will be requested. During the assent/consent process, guardians will be advised that the law requires reporting of child abuse. When appropriate, these reports will be made as soon as possible, but no later than 24 hours after the visit. Our consenting procedures, which demand both consent and assent from guardians and child participants, will help ensure that no underage individuals can enroll without parental support. However, given that participation will result in compensation and children are a vulnerable population, it may be the case that adults could coerce children, who would otherwise not assent, to participate. To account for this, several measures will be taken: 1) researchers will talk to children directly during the telephone screening to ensure assent separate from that of parents, 2) researchers will obtain assent during the first session within sight of but distanced from parents so as to limit the degree of non-verbal coercion that may be communicated during the process, 3) assess the child’s comfortability between each study procedure on a scale from 1 to 10, with scores below 8 meriting further inquiry as to the source and scores below 5 motivating conversations surrounding ending the session early. All study staff will receive training to be especially attuned to coercive behavior from guardians that might influence the decisions of participants and how to handle them.

**Risks to privacy of individuals or confidentiality in data.**

Risks to confidentiality are negligible, because all data (behavioral and imaging) is de-identified and has no information that could link the data back to an individual subject. Risks of privacy of individuals or confidentiality in the data is minimized by (a) identifying subjects based on a generated subject identifier number; and (b) keeping the master sheet linking names to subject identifiers protected on a secure network that requires a personal login and an additional password to access. In compliance with the NIH data sharing initiative, imaging data without any personal information attached may be shared with other investigators or public data repositories. This provides the research community with open access to datasets contributed by labs around the world. Any data that is shared will be completely anonymized with only demographic information about age, gender, handedness, and group membership provided.

**Potential Benefits of the Proposed Research to Human Subjects and Others**

The proposed investigations in normal subjects are unlikely to provide any direct benefit to the participants. Some participants may be motivated to participate by virtue of the reward (credits/monetary compensation), and others might be motivated by a desire to contribute to the understanding of cognitive function. Participants also will indirectly benefit from knowing that they are contributing to research that can improve the understanding of typical cognitive development and potentially advance treatments of neurological and psychiatric illnesses.

**Importance of the Knowledge to be Gained**

Knowledge gained from the findings of the proposed research will be substantial in three respects. First, our research will enhance our understanding of the developing mechanisms behind certainty judgment formations, which may speak towards the existing literature finding associations between high intolerance of uncertainty and negative developmental outcomes. Second, findings from the proposed research will add to our knowledge of certainty self-regulation efficacy and techniques, which may be especially pertinent to mitigate the effects associated with ambiguity or uncertainty aversion. Third, knowledge on how domain-specific certainty judgments may be will inform literature on cognitive decision-making. These potential benefits will far outweigh the minimal risks associated with the proposed studies.

**ClinicalTrials.gov Requirements**

The present study is not a clinical trial and therefore does not need to be registered in ClinicalTrials.gov according to the reporting requirements of Public Law 110-85.