**PRINCIPAL INVESTIGATOR: Theodore D. Satterthwaite, MD, MA**

**PROTOCOL TITLE:**  **Mapping Mood Variability Using Mobile Phenomics and Neuroimaging**

**INTRODUCTION AND PURPOSE:**

The study of mood and anxiety disorders greatly relies on the use of retrospective mood interviews to measure affective variability as well as other symptoms and behaviors. The present study seeks to more accurately measure affective variability using ecological momentary assessment (EMA) and other data collected from participant smart-phones. This data will be used to better characterize mood lability across psychiatric diagnoses, as well as to relate these patterns of behavior to multi-modal network based imaging measures.

**OBJECTIVES:**

This study will be accomplished according to the following two specific aims:

**Aim 1**: To delineate trans-diagnostic mood variability using mobile phenomics.

*Hypothesis 1:* Youth with mood variability as measured by EMA will have a) greater variability in patterns of movement measured by both accelerometer and GPS, b) more irregular circadian cycling.

**Aim 2:** To characterize individual differences associated with mood variability using advanced multi-modal, network-based imaging techniques.

*Hypothesis 2*: Mood variability as measured by EMA will be associated with diminished structural and functional network segregation; network abnormalities will mediate the relationship mood variability and irregular mobility patterns.

**BACKGROUND:**

Notable limitations are present in most existing studies regarding the use of retrospective mood interviews. Symptom burden in individuals with psychopathology have been typically evaluated using retrospective interviews, where participants are asked to recall their emotions over the past week or longer. These measures are increasingly recognized to be both inaccurate and biased, and may be especially problematic in individuals with psychopathology, and especially in adolescents (Baldwin et al., 2019; Hufford, 2007). Mobile phone technology combined with other clinical measures has the potential to offer research a wealth of additional information on clinical phenotypes and symptoms (Solhan et al., 2009). Because the majority of the adolescent and adult populations in developed nations now own and operate smartphones, measurement can be carried out in naturalistic settings in situ leveraging the actual real-world experiences of patients.

Previous work has linked mood lability to aberrations in actigraphic patterns and circadian rhythm in small populations. (McGowan et al., 2020). In this study, we will use a combination of mobile-based ecological momentary assessment (EMA) in a large sample of youth to understand how affective variability present across mood and anxiety disorders is related to patterns of movement, sleep, and other symptoms. Furthermore, we will delineate the neural antecedents of affective variability in a subset of youth using advanced non-invasive, multi-modal imaging.

**CHARACTERISTICS OF THE STUDY POPULATION:**

***1. Target Population and Accrual:***

We aim to enroll 2000 participants, ages 13 to 25 with mood variability to complete virtual procedures. Parents or guardians of minor participants will also be enrolled in the study as participants, to collect data on actigraphic patterns of parent-child diads. A subset of 500 participants will be asked to come in for in-person non-contrast agent MRI procedures.

***2. Key Inclusion Criteria:***

All Subjects

* Age: 13-25. This age range allows us to focus on the critical period of adolescence and young adulthood.
* Sex: Males and Females
* For MRI studies, women of child bearing potential must verbally attest that they are not pregnant at each visit
* Proficiency in English, as study assessments and tasks are designed for English speakers
* Able to understand study procedures and agreeing to participate by giving written informed consent

***3. Key Exclusion Criteria:***

All Subjects

* Significant medical or neurological illness that in the PI’s judgment may increase risks of the study, significantly affects brain function or otherwise impedes participation.
* Pregnancy. Although there are no known risks related to MRI on pregnant women or a fetus, there is a possibility of yet undiscovered pregnancy related risks. Since there is no possible benefit from participating in this protocol for a pregnant woman, we will exclude pregnant women. As in accordance with current guidelines from CAMRIS, we will assess pregnancy by verbal attestation from participants that they are or are not pregnant
* Any history of pervasive developmental disorder or intellectual disability
* Documented history of a psychotic disorder, bipolar disorder, or clinically significant current substance misuse
* Non-psychiatric medical disorders that may impact brain function or visual acuity
* Lack of a mobile device with capabilities to complete study procedures
* Acute intoxication with alcohol or other substances based on clinical assessment, subject report, or results of laboratory testing

Current nicotine use and past substance use will be assessed and their effects examined with covariate and sensitivity analyses.

Note: Race, ethnic origin, or economic status will not be considered in selection of study participants, and the distribution will therefore reflect the diverse population found in the surrounding community.

3T Imaging exclusion (only for 3T imaging visits) – Claustrophobia, or metallic implants that are a contraindication to MRI.

7T imaging exclusion (only for 7T imaging visits) – Any “Undefined” metallic implant or foreign bodies (FB) inside the subject/participant, any life assist, bone growth, or pain management devices or instances where portions (remnants) of that life assist device remain in subjects (e.g. pacer wires), any structural support devices, screws, or wires in bone that are near the spinal cord or temperature sensitive organs (e.g. Harrington rods), reconstructive metallic implants near the orbits, external devices, medicinal patches, piercings, and in most cases jewelry that cannot be removed, any other contraindication to MRI.

***4. Subject Recruitment and Screening:***

Subjects will be recruited via a variety of means, including posted notices on- and off-campus, Penn’s SBSI platform, announcements on the lab website, social media (Twitter, Facebook, Instagram), online electronic newsgroups, text/email/phone or newspaper advertisements.

Participants will also be identified from CHOP/Penn medical record review. This may be conducted manually by study coordinators, or CHOP/Penn reporting units may be asked to generate reports from medical records to identify eligible participants based on a list of inclusion/exclusion criteria. Having a list of eligible participants pulled from medical records via CHOP/Penn reporting and bioinformatics teams is not only more time efficient, but also reduces the need for study staff to personally access medical records and potential participant information unnecessarily, thus increasing patient privacy protections.

Participants also may be identified through the Brain Behavior Lab’s registry of previous research participants who have consented to be re-contacted about participating in future research, or by clinician referral from physicians within the Penn Medicine/CHOP system.

Participants who are interested in joining the study will be directed to an electronic consent form on REDCap. Only if the potential participant (or parent of adolescent participant) indicates that they meet eligibility criteria will they be allowed to consent or assent to study participation. Only after indicating consent to the study will personally identifiable information be collected. Adult participants will give consent to participate. The parents of adolescent participants will give consent to have their adolescent participate and adolescent participants will assent to participation in order to be included in the study.

After consent, participants will be directed to download the AWARE app and follow study-instructions through this mobile app, as well as links to complete the REDCap self-report measures and computerized neurocognitive battery.

A 500-person subsample will be contacted by phone, text, or email (if the subject indicates a preferred method of contact) and informed of the research opportunity to participate in the fMRI in-person visit. A trained coordinator will use IRB-approved scripts for this recruitment call/email (see attached). Phone scripts also include templates for confirmation calls. We will utilize phone-screening procedures that have been used in already approved protocols such as #810336, #813943, and #822831.

## ***5. Early Withdrawal of Subjects:***

Participants may withdraw at any time for any reason, or may be withdrawn early at the discretion of the investigator. After completing the baseline survey participants have the option to not be re-contacted to complete follow-up survey(s). Withdrawal reasons may include, but are not limited to, if the participant is unwilling or unable to complete study procedures, or if they are lost to follow-up.

***6. Vulnerable Populations:***

Participants will receive information and consent detailing the research and its goals. Study coordinator contact information will be provided for the purpose of answering any questions. For minors, the process includes the child and the parent(s). After full examination of all the research procedures and reading the consent form, informed consent will be obtained from the participant. For participants ages 13-17, assent will be obtained from the child/adolescent in addition to parental consent and permission. Information and consent forms will clearly detail the voluntary nature of the research, its distinction from other clinical care, the right to withdraw without penalty, and the steps to be taken to protect confidentiality of information.

Pregnant women, fetuses, neonates, or prisoners are not included in this research study. The study will include adolescents and young adults between the ages of 13 and 25 years of age.

***7. Populations vulnerable to undue influence or coercion:***

For virtual procedures, participants under the age of 18 must have a parent or legal guardian consent for their participation in the study. This will ensure that parents/legal guardians can assist young adults in understanding the informed consent procedures including answering any questions, informing them of the voluntary nature of the research study, their rights to withdraw without penalty and the steps taken to protect confidentiality of information. Only after researchers receive both the parental informed consent and the child assent will the child be eligible to participate in the virtual portion of the research study.

When participants ages 13-17 come in for the in-person MRI procedures, research staff will review the informed consent document section by section with each prospective participant. This process will be done in the presence of a witness, often another family member, research staff person, or clinician. Participants will be given the option of reading through the document himself/herself, or having it read to him/her, as an initial step toward explanation of what participation entails. Participants' questions will be answered throughout. The research staff will take care to explain fully the following issues: the voluntary nature of the research, its distinction from other clinical care, the right to withdraw without penalty, and the steps to be taken to protect confidentiality of information. If there is reason to suspect that the participants mental state is impaired enough to cast doubt on the validity of the statement of consent or assent, they will not participate.

**STUDY DESIGN:**

This an experimental study that will include data collection through both virtual and in-person measures. We will enroll 2,000 participants ages 13-25 for virtual procedures that will include the collection of self-report questionnaires, a neurocognitive battery assessment and both passive and active mobile data collection on the custom-built AWARE App (please see the full description detailed below). This will include 2, 2-week periods of active survey collection 4 times per day, and passive data collection using the AWARE app for 6 months. A subset of 500 participants will be asked to come into the University of Pennsylvania for imaging procedures. This visit will last approximately 2-4 hours and will be conducted at Penn/CHOP. The study design will allow the research team to investigate the relationship between mobile-based ecological momentary assessment (EMA) and other measured patterns of movement, sleep, and other symptoms, as well as brain development as measured by multi-modal imaging data.

**STUDY TIMELINES**

This is projected to be a 4-year study, with start date contingent upon IRB approval and an end date four years after approval (i.e., late 2024). From the time of enrollment, 2,000 participants will partake in the mobile portion of the protocol for up to 6 months. A subset of 500 participants will be asked to participate in a 2-3 hour imaging visit.

**METHODS:**

***1. Study Instruments:***

* Daily Activity Tracking and Monitoring:
	+ Questionnaires similar to those approved in IRB protocol #813943
	+ GPS Data
	+ Accelerometer/activity data
	+ Sociability metadata
	+ Overall phone/screen usage
* Cognitive Assessment
	+ WebCNP Cognitive Battery approved in IRB protocol #813943
* Self Report Questionnaires
	+ Measures approved in lab-wide protocols, including but not limited to:
		- Affective Reactivity Index (ARI)
		- Beck Depression Index II (BDI)
		- Adverse Childhood Experiences scale (ACES)
		- Behavioral Inhibition/Activation Scales (BIS/BAS)
		- Brief Sensation Seeking Scale (BSS)
		- the Chapman Trait Anhedonia Scales for physical (RPAS) and social (RSAS) anhedonia
		- Positive and Negative Affect Schedule (PANAS)
	+ Other standard psychological scales may be administered as well
* Imaging Procedures: All imaging procedures will be approved by CAMRIS. The imaging measures collected in this study will not make use of IV contrast agents.
	+ 3T Imaging Procedures similar to those approved in IRB protocols #828424, #822831:
		- High-resolution Anatomical Images
		- Resting Perfusion Images
		- Functional Images
		- Diffusion Images
		- Other experimental imaging sequences that may not be FDA-approved but are considered non-significant risks
	+ 7T Imaging Procedures similar to those approved in IRB protocol #825834:
		- Magnetization prepared rapid gradient echo (MPRAGE) resulting in a T1-weighted contrast image
		- Spoiled gradient echo (GRE) resulting in a T2\*-weighted contrast images
		- Turbo spin echo (TSE) sequence resulting in T2-weighted contrast
		- fMRI BOLD activation to a white cross-hair
		- Single-shot echo planar imaging (EPI)
		- GluCEST imaging parameters
		- Other experimental imaging sequences that may not be FDA-approved but are considered non-significant risks

## ***2. Group Modifications:***

## Age appropriate assessments will be used for each age group.

***3. Method for Assigning Subjects to Groups:***

Sub-cohorts based on mood/anxiety status may be identified by a brief self report survey based on structured interviews approved in protocols #831819, #828424, and others.

 ***4. Administration of Surveys and/or Process:***

Surveys will be collected electronically via the AWARE app or REDCap. The AWARE surveys will be presented via mobile phone 4 times per day for a two-week duration. These surveys will take about 10 minutes to complete. The survey will not collect names, and will only include a minimal number of identifiers (i.e., zip code, IP address, date/time of collection, email address). Participants may only be asked to complete the survey once, or may be asked to provide repeat information at a later stage. Additional information if needed may also be collected via secure, password protected data capture platforms such as REDCap.

## ***5. Data Management:***

As in IRB approved protocol #829744, data sharing procedures will be clearly explained to all participants within the consent forms before they give consent for us to collect their information. Data will be provided to this facility without personal identifiers. Furthermore, the consent states that de-identified data may be shared with other scientists currently not included within the current research team. De-identified data may be shared through public archives including National Data Archive, OpenNeuro, and Indie International Data Sharing Initiative, or others not yet created. Notably, participants and parents are informed that while they can choose to withdraw their data from the study, data that has already been shared cannot be deleted or retracted. Participants will not be compensated from any commercial products developed using openly shared study data.

***7. Subject Follow-up:***

## From the 2,000 participants initially enrolled in the virtual procedures, a subset of 500 participants will be re-contacted to gauge if they would be interested in completing an in-person study visit to the University of Pennsylvania. In the event that the participant is under the age of 18, a legal guardian or parent must speak with the minor and help to coordinate scheduling of the second visit, and consent into the imaging procedures of the study.

## **STUDY PROCEDURES:**

***1. Detailed Description:***

A total of 2,000 participants will be recruited to participate in mobile phenotyping procedures (detailed below), self-report measurements, and computerized assessments. A 500-person subset of this group will be brought to the University of Pennsylvania and given a separate consent form for an in-person MRI scan. The following procedures will primarily be completed electronically, but may be completed in person during pilot testing.

1. Consent to Screen & Eligibility Questions

Participants will complete a short consent form followed by a short self-report screener that will act to ensure that they meet preliminary inclusion criteria. If a participant is eligible they will then be directed to the full-length consent form for enrollment into study procedures.

2. Information/Consent Form

The form provides the information about the study in a clear and concise manner so the participant can make an informed decision about their participation. Participants confirm their consent by selecting ‘agree’ on the form. Participants cannot continue the survey unless they select ‘agree’. The first question of the survey acts as a screener, and asks the participant if they are over the age of 18. Participants who respond they are under the age of 18 will not be able to continue the survey and start the study until they receive parent/guardian permission (further information regarding the consenting process is detailed below). The virtual consent/assent will be obtained for all virtual study procedures including the daily activity tracking and monitoring, self-report questionnaires, and computerized neurocognitive battery. A separate, in-person imaging consent/assent will be obtained when participants come to the University of Pennsylvania for the in-person MRI procedures.

3. Daily Activity Tracking and Monitoring

Included in the virtual consent/assent, participants will be asked to install the study-specific AWARE app on their personal smartphone and keep this app on their phone for the duration of the study. The custom app, developed using the AWARE platform by researchers at Penn, passively collects information about location (GPS), physical activity/movement (GPS/accelerometer), phone call and text messaging meta-data, app usage, and overall phone/screen usage. For phone call and text messaging data, AWARE does not collect personal information such as phone numbers, or contact information. A unique ID is assigned to each contact that is irreversible (SHA-1 encryption), but it is always the same for the same source. Study staff will ensure that participants are fully informed of the measures to be collected via the AWARE app.

The AWARE app is developed in part by collaborators in the Department of Bioengineering at Penn (Professor Lyle Ungar, study co-investigator). Identical procedures using AWARE have been previously approved by the Institutional Review Boards of the Perelman School of Medicine at the University of Pennsylvania (#832546); previous studies from our group have collected identical data using similar procedures and a different app (Beiwe) developed by collaborators at Harvard (#813943).

For the current study, as part of the ecological momentary assessment (EMA), we will sample responses 4 times per day for two 2-week periods. EMA will include questions related to mood, behavior, sleep, or other aspects pertaining to participants’ daily lives. To measure fine scale changes in effect, EMA allows us to ask a participant “how do you feel now?” repeatedly, rather than query in a face-to-face interview “how have you felt on average over the past week?” The AWARE platform thus will enable dynamic measurement of mood fluctuations. Surveys distributed will be similar to questionnaires approved under protocol #813943.

All surveys appear as screens within the app. The app will show a notification in the notification bar, reminding participants to fill out each survey various times a day, at times selected by the participant. Answering a survey in the AWARE app is never mandatory. If the user presses the Home or the Back button, the survey is dismissed, and the status (new, dismissed, expired, branched or answered) of each survey is tracked by the study. The participant does not need to take the survey immediately upon notification, and can wait until he or she is in private to do so. The study will remain in the participant’s app dashboard for until it is taken, or for an amount of time specified by the researchers. AWARE records not only the participants answer to survey questions, but also the amount of time the participant took to answer each question, and any intermediate answers the participant may have selected.

After completing each survey, the participant is reminded that a clinician will **not** review the responses, so the survey **cannot** be used to communicate with study staff or to request help. The reminder will also state that if the participant needs to get in touch with either his/her clinician or the research study staff, they can select an option to display phone numbers to contact their clinician (if they are receiving clinical care), a hospital or crisis response center, or study staff. These phone numbers are entered during the registration and study enrollment process, and emergency contact numbers will be displayed automatically.

In addition to survey data, AWARE allows us to passively collect information pertaining to accelerometer data, GPS data, phone call and text messaging meta-data (but not content), and phone/screen usage data. This passive data will be collected for up to 6 months.

Regarding accelerometer data, the AWARE app measures the acceleration applied to the sensor built-in into the device which indicates movement of the phone and can be used to gauge the physical mobility of participants, such as activity type (sitting vs. walking) and extent of activity (e.g., number of steps taken). For GPS data, the AWARE app provides the best location estimate for the users’ current location, automatically, based on latitude, longitude, bearing and speed (if available) in degrees, along with an estimated accuracy of the location. GPS data can be used to construct what are called *mobility metrics*: summary statistics that characterize a person’s mobility patterns, such as daily distance traveled. For phone call and text messaging data, communication events such as calls and messages, performed by or received by the user. This sensor **does not** record personal information, such as phone numbers or contact information. Instead, a unique ID is assigned that is irreversible (SHA-1 encryption) but it is always the same for the same source. For phone/screen usage, AWARE records when the phone’s screen turns on or off, is locked and unlocked along with the timestamp. Screen use information can serve as a proxy for when the participant is using their phone.

Participants will be provided a handout that has information and instructions related to the AWARE application (see attached).

4. Self-Report and/or Interview Assessments of Symptoms, Experiences, or Personality Traits

Under the virtual consent/assent, several brief self-report measures will be administered to allow more detailed assessment of the areas of particular relevance to this study. A link to the REDCap self-report measures will be sent to the participant via email after completion of the eligibility screener so all questions can be answered remotely. All proposed measures are part of a larger battery of assessments from previously approved protocols within the Brain Behavior Laboratory (#813943, #822831, #828424).

5. Computerized Neurocognitive Battery Procedures

As a part of the virtual procedures, a link to the Neurocognitive assessment will be sent to the participant after completion of the eligibility screener which allows the participant to complete the computerized neurocognitive battery virtually.

The Brain Behavior Laboratory center-wide protocol #813943 explains the standard cognitive assessment participants may receive using a computerized neurocognitive battery (CNB), which has been extensively applied in our studies, and lasts about 1 hour.

6. MRI Study Procedures

After signing a separate imaging consent form in-person, participants will be asked to come in to the University of Pennsylvania for MRI procedures. Studies using a 3T MRI scan will take place at either the HUP 6 Scanner, in the basement of the Rhoads Building at the Hospital of the University of Pennsylvania, or on the 3T Prisma located in the basement of the Stellar Chance Laboratories in the University of Pennsylvania. Studies using a 7T MRI scan will take place at Stellar-Chance 7 (STC7) Scanner, which is located in the basement of the Stellar Chance Laboratories in the University of Pennsylvania. MRI visits will take 2-3 hours.

*Preparation for MRI*: Brief practice versions of scanner tasks will be conducted out-of-scanner in order to ensure all subjects understand and can perform the tasks. In addition, as previously approved in protocol #829744, if necessary a mock-scanning session will be conducted inside a decommissioned MRI scanner in order to ensure to acclimatize the subjects, reducing novelty and anxiety responses inside the scanner. Participants will then be prepared for scanning by a study coordinator and the MRI technician or certified Level II MRI operator. Participants will fill out a brief self-report scale to assess anxiety and mood symptoms before the scan. Subjects will be placed supine in the scanner, wearing earplugs to muffle noise. Head fixation will be ensured by foam rubber mounted on the headcoil, which we have found provides excellent motion control even in motion prone individuals. Stimuli are rear projected to the center of the visual field and viewed through a mirror mounted on the head coil. Participants are given a color-coded response device made of non-ferromagnetic components (FORP™ Current Design Inc., Philadelphia, PA), which they use to provide responses to the in-scanner tasks.

7. Medical Record Review

Information may be collected from CHOP or Penn medical records for as long as data analysis continues. This information may include name, date of birth, contact information, results of tests and procedures, medical record number, and medical and mental health history.

***2. Data Collection:***

Data sources may include:

• Medical/mental health records at Penn and CHOP

• Medical/mental health records external to Penn and CHOP

• Data collected at the study visit from questionnaires, interviews, neurocognitive batteries, imaging procedures etc.

• Smartphone data collection, including GPS data, etc collected from the AWARE app

• Relevant data from studies at Penn/CHOP in which participants have previously participated

When relevant and available, data may be shared from other studies to be included in analysis, including neurocognitive and clinical assessment data.

***3. Genetic Testing:***

This study will not be performing genetic testing.

***4. Use of Deception:***

This study will not use deception.

**5. Statistical Analysis:**

The analysis plan for each aim is described below.

**Aim 1:** To delineate trans-diagnostic mood variability using mobile phenomics.

Affective variability will be summarized as the root mean squared differences between EMA assessments over the two week period of active mobile phenotyping. Passive measures such as actigraphy and GPS will be summarized as “mobility” metrics will be summarized according to measures developed by co-Investigator Ian Barnett in the Department of Epidemiology and Biostatistics (Barnett & Onnela, 2020). Associations between affective variability and mobility metrics will be evaluated using generalized additive models with penalized splines to account for linear and nonlinear effects.

**Aim 2:** To characterize network level abnormalities in youth with mood and anxiety disorders associated with mood variability using advanced multi-modal, network-based imaging techniques.

Functional and structural connectivity data will be processed using highly reproducible, top-performing pipelines developed by our laboratory and our collaborators. These include fMRIPrep, the eXtensible Connectivity Pipelines, and QSIPrep (Ciric et al., 2018; Cieslak et al., 2020). Detection of community structure yields a multi-modal network partition for each participant, as well as an estimate of the modularity quality index (*Q*). This statistic will function as the summary index of network modularity; higher values of normalized *Q* indicate greater separation of brain regions into modules. As each individual’s network partition is expected to vary, we will also derive a consistent across-subject partition using an iterative consensus clustering procedure. In the consensus partition, the quality of each module (*Qmod*)will be calculated both within and across modalities; use of a consensus partition for analysis of individual network modules will ensure across-subject correspondence of modules. For regional analyses, we will calculate the participation coefficient (*PC*), which measures the balance of within- *vs.* between-network connectivity. This procedure yields multi-modal network segregation (*Q*) and integration (*Eglob*) for each subject. Associations with affective variability across mood and anxiety disorders will be tested using GAMs as above. For higher-resolution analyses of module-specific (*Qmod*)and regional segregation (*PC)*, we will apply an FDR (Q<0.05) correction for multiple comparisons. Mass-univariate connectivity analyses will complement such network measures.

**RISK/BENEFIT ASSESSMENT:**

***1. Risks:***

***General risks:***

Fatigue, anxiety and discomfort are potential adverse effects associated with the tasks, symptom assessments, or other aspects of the study, but not more so than encountered during the performance of routine physical examinations or tests. Subjects (if 18 years old or older) will be asked about past traumatic experiences that they may have had. These questions may cause discomfort for individuals. Subjects will be informed that they can refuse to answer any question that makes them uncomfortable. Subjects will also be made well aware that they can continue participation in the study even if they refuse to answer certain questions. Minors (if under 18) will not be asked these questions about past traumatic experiences.

As with many research studies, there is a risk of loss of anonymity through data analysis. While all participant identifiers will be de-identified through use of unique identification numbers, the richness of the data permits someone skilled in the art to re-identify the data. To guard against this, all researchers accessing the data must undertake to not knowingly perform that kind of analysis, and to never report individual data where re-identification might be possible (e.g., longitudinal GPS traces) without signed consent of the participant. This risk will be managed by ethical conduct of all researchers involved, deep (multiple layers) of encryption as described previously, and through informed consent, which will explicitly detail that absolute anonymization is not possible.

***Risk associated with text message, EMA, smartphone sensing, and smartphone data collection:***

Survey and EMA data collection via RedCAP will be done in accordance with protocol 828424.The sensor data being collected is already being recorded by individuals’ smartphones. However AWARE Research Platform takes additional measures to ensure data security.

1. **Key security aspects of the AWARE Research Platform**

Participant names are not used. Instead, study staff will use a unique 8-character AWARE Participant ID.  Research staff loads the app onto the phone and will login to the AWARE smartphone application with the assigned unique ID and password.  All data collection is tied to this 8-character AWARE Participant ID (no identifiers like participant name or contact information), and only research staff will have access to the master key, which will be stored securely. All data is encrypted in transit and at rest. The application will not store data on the participants’ mobile device in an unencrypted form. Indirect identifiers (telephone numbers and IP addresses) will be hashed using an industry recognized strong hashing algorithm, which renders all data unidentifiable. No identifiable data will be stored on the mobile device. All identifiers will be rendered innocuous by hashing.

1. **Data Anonymity**

Every participant is assigned a randomly generated 8-character participant ID (for example, “d4w192bg”), and all participant data are connected only to that ID. Phone numbers of incoming and outgoing phone calls and text messages and MAC addresses or nearby Wi-Fi routers and Bluetooth devices are hashed by AWARE using the industry-standard SHA-256 hashing algorithm:

Hashing these data means that each phone number and MAC address gets turned into a string of 32-character random numbers and letters, but a certain phone number always gets transformed into the same random string. It’s also impossible (under present-day mathematical theory) to undo a hash. Imagine that participant D4MAAW called the phone number 617-123-4567 once on Monday, and then received two calls from that same phone number on Tuesday. A researcher analyzing the AWARE data could see when those three calls happened and could tell that they all involve the same phone number but couldn’t tell what that phone number was. Hashing the MAC addresses of Wi-Fi routers has the same effect. A researcher analyzing AWARE could tell that a participant was near a certain Wi-Fi router at 10am on every morning, Monday through Friday, and could thereby surmise that the participant was probably in the same room at 10am every morning, Monday through Friday, but the data would not reveal the actual MAC address of the router.

## ***MRI studies:***

The known risks associated with MRI studies are minimal. The levels of energy used to make magnetic resonance measurements are far less than are used in a single X-ray, and many patients have been safely studied using magnetic resonance techniques. The radio waves and magnetic fields, at the strengths used, are felt to be without harm. This study may include the use of custom manufactured head coils and experimental imaging sequences that are not FDA-approved but are considered non-significant risks. There are no known health risks associated with exposure to magnetic fields during an MRI, and the FDA has approved the use of 7T MRI scanners for diagnostic use, and considers magnetic field strengths up to 8.0T to pose no more than minimal risk. Because the magnetic field of the MRI scanner attracts metal, the greatest risk is a metallic object flying through the air toward the magnet and hitting the participant. To reduce this risk, we require that all people involved with the study remove all metal from their clothing and all metal objects from their pockets. No metal or magnetic objects are allowed in the magnet room at any time. Participants will be asked to place all metallic and magnetic objects in their possession (e.g. keys, jewelry, credit cards) in a locker outside the magnet room. In addition, once the participant is in the magnet, the door to the room will be closed so that no one inadvertently walks into the magnet room. Individuals will not be permitted to participate in the study if they have electrically, magnetically or mechanically activated implants such as cardiac pacemakers, clips on blood vessels in their brain, or other metallic objects in their body such as permanent retainers, orthopedic pins or plates, shrapnel, bullets, buckshot, or metal fragments. A checklist will be given to the participant before entering the MRI room, which will be reviewed and used to verify that they do not have any non-removable metallic objects or implanted devices in their body prior to participation. Most people do not find an MRI scan uncomfortable. However, on occasion some subjects have reported mild discomfort. The following are some types of discomfort that have been reported. The MRI machine is noisy, because of the knocking and beeping sounds that resonate when the magnetic gradients are pulsed. All participants will be given disposable earplugs or padded headphones to reduce the noise. Also, some people have reported feeling claustrophobic in the MRI machine. Participants will be made aware of this possibility, and we will ask individuals to refrain from participating if they tend to experience feelings of claustrophobia. If subjects become uncomfortable inside the magnet, they may withdraw immediately from the study. During some of the MRI scans, some subjects have reported temporary dizziness upon being moved into the field. This dizziness lasts less than 10 minutes. Also, some people have reported a metallic taste in their mouth, which can be associated with fillings in their teeth. Finally, due to the rapid rate of change of the magnetic gradients during imaging, the possibility exists for peripheral nerve stimulation. If this happens, subjects may feel a tingling or twitching sensation, typically along their arms or legs. This sensation is temporary, and stops when the scan ends. Participants will be instructed to notify the research staff if, at any time, they feel uncomfortable, no matter what the reason. Participants will be in contact with the research staff throughout the study through a microphone mounted on the MRI scanner. Participants will also be instructed in how to use an emergency handheld device to inform the operator if they wish to immediately stop scanning and be removed from the magnet. Scanning can be stopped at any time at their request. Participants will be informed that they should contact the PI if they have experienced a research-related injury. Although there are no known risks of MRI on pregnant women or a fetus, there is a possibility of yet undiscovered pregnancy related risks. Since pregnant women receive no direct benefit from participating, we will exclude pregnant women from this study. A negative urine pregnancy test or verbal attestation to non-pregnancy will be mandated before a woman of childbearing potential can participate in the imaging segment of this study.

***2. Benefits:***

There is no direct benefit to participants for participating. However, over the long term, we anticipate that the novel results produced by this research program may potentially be useful in deploying targeted early interventions for youths with affective variability in the context of mood and anxiety disorders in order to achieve better and more durable outcomes. In future clinical trials, individuals with these kinds of disorders may be stratified based on brain imaging phenotypes to predict response to both psychological (e.g., therapy) and pharmacological interventions. Participants may obtain some gratification in participating in research they consider of value to others. The minimal risks to subjects are reasonable in relation to the anticipated benefits to others.

***3. Subject Privacy:***

For all virtual study procedures, where the participant chooses to complete the surveys and the neurocognitive battery is at discretion of the participant. Research survey data will be stored on password protected databases (e.g. REDCap), AWARE application, servers, and shared drives, accessible only to study staff. Participants will be informed that results are for research purposes only, and any publications will not include identification of individuals. Every attempt will be made by the investigators and study staff to maintain all information collected in this study remains confidential. Only a minimal number of identifiers are collected as part of the online assessment to be included within the databases. Any other identifiers collected as part of medical record review will be stored in a separate, secure database that is accessible to only essential study staff to increase data security and limit PHI collected in the online survey.

For in-person study procedures, Consent and assessments will be conducted in private assessment rooms by trained study staff to protect participants’ privacy. Consent may also be collected electronically via REDCap and University approved video conferencing platforms (e.g. BlueJeans or Zoom).

## ***4. Subject Confidentiality:***

**How will confidentiality of data be maintained? Check all that apply.**

[x]  Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.

[x]  Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.

[x]  Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.

[x]  Whenever feasible, identifiers will be removed from study-related information.

[ ]  A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject’s financial standing, employability, or liability.

[ ]  A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.

[x]  Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.

[ ]  Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.

[x]  Other (specify): See text below.

Each participant in the study will be given a unique ID number. This number will be used to label all private research information, including clinical assessments and biomaterials. All study data and all personally identifying information (e.g., name, address) will be stored in secure physical files and electronic databases accessible only to authorized study staff. If any data is released outside of the study team they will be de-identified before release.

Basic demographics and test data collected during the CNB are transferred in encrypted format to a secure server. Access to the server is through a password-protected account that allows access to data collected only to the investigator and their designees.

Data for this protocol is to be collected and managed using REDCap and Oracle electronic data capture tools hosted at the Brain Behavior Laboratory, University of Pennsylvania. These databases run on a secured server. The drive is encrypted and the system is housed in a secured room with controlled and monitored access on the University of Pennsylvania Health System Campus. The server is connected to a public network (PennNet) and protected by a built-in software firewall (IPFW). All unnecessary services are disabled. Access to the databases are secured using unique usernames and passwords. All study personnel must receive PI approval for access to the databases.

Text Message (SMS) data will be stored in accordance with Protocols 816091, 824588, and 827356. Text message data sent from the consenting participant is collected, we do not collect text data sent *to the participant* from non-consenting individuals, nor do we store their phone numbers or any identifying information. We will divorce the server that serves the application to the user (application server) from the infrastructure which collects and protects identifiable user information (secure server or secure data repository). Both servers will be housed and under the control of the University of Pennsylvania, such that no data we collect will be stored out of our control. Additionally, the secure data repository will be "write-only" from the application server, so the application itself will not even be able to access identifiable information.

Data collected through the AWARE app on participants’ smartphones, including passive sensing data and EMA data, will be transferred to and stored on a secure server. The server will stored on a local server behind Penn’s firewall, which requires a VPN to access, managed by PMACS and the Penn Lifespan Informatics and Neuroimaging Center. AWARE uses a store and forward data management architecture. This means that the app initially buffers data on the device, and when a Wi-Fi connection becomes available, AWARE sends the data to the secure server. All data is encrypted while on participants’ phones and when in transit to the secure server. Participants will be assigned an AWARE Participant ID. No identifiers, like participant name or contact information, is either collected or stored within the AWARE app or on the server. Only research staff will have access to the study specific master key, which is stored securely. AWARE does not store personal information such as phone numbers, contact information, or call/message content. AWARE encrypts this personal information using a one-way hashing (SHA-1 encryption). Access to pull data from the secure server will be severely restricted (through password-protected SSH key files), and only the senior researchers in the group will have the access to the data.

AWARE does not collect personal information such as phone numbers, contact information, or call/message content. When a participant receives a phone call or text message, a unique ID is assigned to each contact that is irreversible (SHA-1 encryption), but it is always the same for the same source. All data collected on the smartphone is tied to an AWARE Participant ID. No identifiers, like participant name or contact information, is either collected or stored within the AWARE app or on the server. All data collected by AWARE is encrypted while stored on the participant’s phone and in transit to the secure server. Participants will be instructed to password-protect their phones.

Basic demographics and test data collected are transferred in encrypted format to a secure server. Access to the server is through a password-protected account that allows access to data collected only to the investigator and their designees. Audio-recorded interviews will be stored on a password-protected computer, transcribed, and then destroyed to eliminate audible identification of subjects.

In publication, presentation, or data sharing resulting from this research, the participants will not be identified.

The study may be terminated at any point, at the subject’s request or upon the judgment of the PIs or study team. If, in the clinical judgment of the PI, or the study team, the participant is found to meet any of the exclusionary criteria, or if the patient shows any potential medical complication at the time of the study, the study will be terminated. In the case of premature termination from the study, the subject will be informed of the need to terminate.

***5. Protected Health Information***

The following will be collected and shared among the study team (described below): Procedures for proper safe storage of PHI are detailed above

* Name, address, telephone number, email address, date of birth and age
* Social Security Number, or last 4 digits of your child’s Social Security Number, will be collected and shared with Greenphire for compensation purposes
* Personal and family medical/psychiatric history including results of tests and procedures
* Family information (parents’ first names, handedness, education level and occupation; number of biological and half siblings, birth order) and family tree, and permission to contact family members
* Sex, handedness (which hand is dominant)
* Race, ethnicity, and sexual preference (all optional)
* Years of education, number of children, occupation, smoking history, allergies
* Information about past hospitalizations, medical record numbers
* Current and past medications or therapies
* Medical Record Number

***6. Compensation:***

Compensation is divided according to study components, as individual subjects may only be asked to participate in a subset of these components. Multiple study components may be completed on a single visit or separated across two or more visits depending on the scheduling requirements of study staff and research participants.

**Payment Procedures:**

Payments will be made using virtual Greenphire ClinCards that may be treated as debit cards. The cards will be assigned and sent virtually to participants. Payments will be made on a weekly or monthly basis.

**Virtual Procedures:**

Activity Monitor Task (AWARE):

Subjects will receive $1 per survey they complete during each of the 2 weeks, with a $3 bonus for completing more than 75% of the surveys (up to $31/week.) Subjects will be paid $3 for each month of passive data collection (detailed below) for 6 months (up to $18).

Computerized Neurocognitive Battery (1 hour): Subjects performing cognitive testing with the standard Computerized Neurocognitive Battery (CNB) applied routinely in the Brain Behavior Laboratory will be paid $20 as detailed in protocol IRB #813943.

Self-Report Measures: (1 hour): Subjects will be compensated $10 for completion of proposed surveys assessments from previously approved protocols within the Brain Behavior Laboratory (#813943, #822831, #828424).

Participants will receive up to $172.00 for all virtual procedures, paid out over a 6 month period.

**Imaging Procedures:**

Assessments of Decision-making, Reward, Motivation, and Sociality (1 hour): $40. This component of the study is not covered under other protocols. It involves performance of one or more laboratory behavioral tests as described below in Procedures. Some of these laboratory tasks may be performed inside the MRI scanner, in which case the MRI compensation described directly below will also be provided. In addition, a set of brief self-report questionnaires and/or interviews will be administered that focus specifically on symptoms, experiences, or personality traits related to decision-making, reward, motivation and/or sociality, as described in the Procedures section of this protocol.

Magnetic Resonance Imaging (1 hour): $60. This component of the study is not covered under other protocols, and involves performance of one or more MRI scans, as outlined below in Procedures. Additionally, subjects may be asked to complete self-report questionnaires and/or interviews, as described in the Procedures section of this protocol.

Participants will be reimbursed for travel (transportation and parking) expenses incurred on scan day.

***7. Data and Safety Monitoring:***

Data and safety monitoring will be conducted by the PI with assistance from the study team, whose members will be fully trained in necessary protocols, procedures and regulatory guidelines. Routine procedures are in place to ensure the safety, confidentiality, and integrity of subjects and data on an ongoing basis.

Data from RedCAP will be stored on secure servers under our control at the University of Pennsylvania, such that no data we collect will be stored out of our control. Access to pull data from the Secure Data Repository will be severely restricted (through 128-bit RSA SSH key files), and only the authorized researchers in the group will have the access to copy the information from the Secure Data Repository to the secure data infrastructure within the Penn Lifespan Informatics and Neuroimaging Center and behind the UPenn firewall. Importantly, the SSH key files on the application server, even if compromised, would not give an intruder access to the Secure Server. All sensitive data will be encrypted in transit (SSL) in accordance with Penn IT policies. Data from RedCAP will also be stored on our secure servers as described above. Data will be de-identified by assigning a unique number to each participant. Only authorized personnel on the study will have access to the document that links the unique subject identifier to participants identifiable information, which will also be stored on our secure server.

Data collected through the AWARE app on participants’ smartphones, including passive sensing data and EMA data, will be transferred to and stored on a secure server. The server will be managed by the Penn Lifespan Informatics and Neuroimaging. AWARE uses a store and forward data management architecture. This means that the app initially buffers data on the device, and when a Wi-Fi connection becomes available, AWARE sends the data to the secure server. All data is encrypted while on participants’ phones and when in transit to the secure server. Participants will be assigned an AWARE Participant ID. No identifiers, like participant name or contact information, is either collected or stored within the AWARE app or on the server. Only research staff will have access to the study specific master key, which is stored securely. AWARE does not store personal information such as phone numbers, contact information, or call/message content. AWARE encrypts this personal information using a one-way hashing (SHA-1 encryption). Access to pull data from the secure server will be severely restricted (through password-protected SSH key files), and only the senior researchers in the group will have the access to the data.

AWARE does not collect personal information such as phone numbers, contact information, or call/message content. When a participants receives a phone call or text message, a unique ID is assigned to each contact that is irreversible (SHA-1 encryption), but it is always the same for the same source. All data collected on the smartphone is tied to an AWARE Participant ID. No identifiers, like participant name or contact information, is either collected or stored within the AWARE app or on the server. All data collected by AWARE is encrypted while stored on the participant’s phone and in transit to the secure server. Participants will be instructed to password-protect their phones.

For online procedures, the study will be completed online on participants’ personal smartphones and computers. For in person visits, all interactions with study staff occur in private testing rooms or staff offices within the PennLINC Laboratory located on the 5th floor of the Richards Building at the University of Pennsylvania. All subjects will be offered to consent to be re-contacted at a later date for participation in another study. When a subject states he/she no longer wishes to be contacted for future study recruitment, he/she is identified as non-active in the database. This non-active status eliminates subjects from database queries and alerts study personnel to not contact this individual. Procedures are in place for protecting the privacy of participants. Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). When a subject is enrolled in a PennLINC study, he/she is assigned a unique identification number that is used to identify all data associated with that person, including hard copy and computerized data. Research data pertaining to specific subjects that is entered into computer databases is de-identified and entered under a 5-digit number that is randomly assigned rather than being connected to any PHI that would directly identify the subject. In any disclosures of study results outside of the University of Pennsylvania Health System, School of Medicine, or CHOP, subjects will not be identified by name, social security number, address, telephone number, or any other direct personal identifier unless disclosure of the direct identifier is required by law or court order. In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts will be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

***8. Investigator’s Risk/Benefit Assessment:***

The clinical self-report measures, neurocognitive battery, and MRI procedures have been administered to many different patient populations and healthy volunteers in both clinical settings and research laboratories. Additionally, the risk of a breach in confidentiality is small. Only a minimal number of identifiers are collected as part of the online assessment and any other identifiers collected as part of medical record review will be stored separately and accessible to only essential study staff. Although there is no anticipated direct benefit to individuals participating in the study, the benefit of furthering our understanding of mood variability and its relationship to structural and functional network segregation outweighs the risks of this study, which are all minimal.

***INFORMED CONSENT:***

***1. Consent Process***

*1. Informed Consent for Virtual Procedures*

Participants interested in joining in the study will first be directed to a short online consent-to-screen form which provides a summary of the research study and asks them to “agree” to the screen. In this section participants will be asked if they are over the age of 18.

Participants who indicate that they are over the age of 18 will then be asked to fill out a brief screener that will determine if they are eligible to participate in the study. Screening mechanisms will be similar to those used by LiBI, a research institute that spans both CHOP and Penn, and Penn’s center-wide common protocol (#813943). For participants who are under the age of 18, they will be informed that a parent or legal guardian must fill out the screener in order to continue.

For participants over the age of 18, if their screener indicates they are eligible for participation in the study, they will be directed to our in-depth online consent form. For adolescent participants, under the age of 18, if parental responses indicate that their child is eligible for participation in the study, they will be directed to our online consent form, in which parents will consent to their child’s participation in the study. Adolescent participants will then provide their electronic assent to participate at the laboratory visit before they are considered enrolled in the study.

Virtual consent/assent will provide participants with an in depth description of the study, the voluntary nature of the research, its distinction from other clinical care, the right to withdraw without penalty, the steps to be taken to protect confidentiality of information. Potential physical risks, and risks involving breach of confidentiality will be emphasized. The virtual consent/assent will be obtained for all virtual study procedures including the daily activity tracking and monitoring, self-report questionnaires, and computerized neurocognitive battery.

*2. Informed Consent for Imaging Study Visit*

For the in-person visit to the University of Pennsylvania participants will be asked to sign a separate consent for imaging procedures. Participants will meet with a trained Research Coordinator who will explain the research and its goals. After full explanation of all the research procedures and reading the consent form, informed consent will be obtained from the participant; however, if there is reason to suspect that the participants mental state is impaired enough to cast doubt on the validity of the statement of consent, they will not participate. For participants ages 13-17, assent will be obtained from the child/adolescent in addition to parental consent. Research staff will review the informed consent document section by section with each prospective participant. This process will be done in the presence of a witness, often another family member, research staff person, or clinician. Participants will be given the option of reading through the document himself/herself, or having it read to him/her, as an initial step toward explanation of what participation entails.

Participants’ questions will be answered throughout. The research staff person will take care to explain fully the following issues: the voluntary nature of the research, its distinction from other clinical care, the right to withdraw without penalty, and the steps to be taken to protect confidentiality of information. Potential physical risks, and risks involving breach of confidentiality will be emphasized. The research staff person will confirm the participant’s correct understanding of each of these issues through appropriate questioning of the participant. If there is reason to suspect that a person’s mental state is impaired enough to cast doubt on their ability to provide informed consent (or assent), the research staff will not proceed and will not include them in the study.

As previously approved in protocol #829744, it is possible that we will also collect consent for the imaging visit and administer a subset of study procedures electronically using REDCap, over the phone, or using BlueJeans or similar HIPAA-compliant, IRB and University approved teleconferencing systems (e.g., Zoom). Following consent, participants will be instructed to print or save the page for their records. This page will not include protected health information.

***2. Waiver of Informed Consent:***

No waiver of informed consent is requested for the present study.

**RESOURCES NECESSARY FOR HUMAN RESEARCH PROTECTION:**

All staff has extensive experience with the studies being proposed, and all will be trained on the procedures of the current study. Moreover, the innovations detailed above leverage an established multi-disciplinary team of investigators, which is already in place as part of an ongoing study of irritability and affective lability (#828424). Dr. Satterthwaite will lead the effort, and provide his expertise in brain development, multi-modal neuroimaging, mood disorders, and developmental psychopathology; furthermore, he has extensive experience with patients with psychiatric disorders and implementing research designs of similar or greater magnitude. Dr. Satterthwaite has multiple collaborators that have expertise in mobile phenomics, network science, machine learning methods, multivariate pattern analysis, high-dimensional neuroimaging statistics and functional neuroimaging; therefore, much collaboration among other researchers will ensue and will ensure proper data collection and analysis. Research assistants working on this project will have experience in administering rating scales and behavioral testing. Assessment and training outside of MRI are performed in the Richards Medical Laboratories at the University of Pennsylvania, which will provide excellent facilities for this research. There is a reception area, intake and examination rooms for daily operations. The proximity to the laboratory facilities (e.g., Neuroimaging) is optimal for research interactions and enhances our ability to have participants undergo multiple protocols. Data management is provided by the Data Core of the Lifespan Informatics & Neuroimaging Center. This includes subject tracking, database management, data entry, data validation and quality assurance.

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