Design and Methods of a Prospective Smartphone App-Based Study for Digital Phenotyping of Mood and Anxiety Symptoms Mixed With Centralized and Decentralized Research Form: The Search Your Mind (S.Y.M., 心) Project

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In this study, the Search Your Mind (S.Y.M., 心) project aimed to collect prospective digital phenotypic data centered on mood and anxiety symptoms across psychiatric disorders through a smartphone application (app) platform while using both centralized and decentralized research designs: the centralized research design is a hybrid of a general prospective observational study and a digital platform-based study, and it includes face-to-face research such as informed written consent, clinical evaluation, and blood sampling. It also includes digital phenotypic assessment through an application-based platform using wearable devices. Meanwhile, the decentralized research design is a non-face-to-face study in which anonymous participants agree to electronic informed consent forms on the app. It also exclusively uses an application-based platform to acquire individualized digital phenotypic data. We expect to collect clinical, biological, and digital phenotypic data centered on mood and anxiety symptoms, and we propose a possible model of centralized and decentralized research design.

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INTRODUCTION

The vast majority of people experience mood and anxiety problems, including a broad spectrum of affective states such as depression, anxiety, fear, anger, excitement, and elation. Among such affective problems, anxiety and manic-depressive issues are expressed as independent compartmentalized psychiatric disorders.[1] According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), pathological anxiety and manic-depressive problems can be classified as anxiety disorders, depressive disorders, or bipolar and related disorders.[2]

The lifetime prevalence of anxiety disorder and mood disorder are about 10% and 15%, respectively.[3-5] Among anxiety symptoms, panic attacks are unique symptoms characterized by a sudden onset of intense fear and anxiety that peaks within minutes, as well as repeated physical symptoms such as palpitations, dizziness, nausea, or sweating. While the prevalence has been gradually increasing in recent years, the prevalence and lifetime prevalence of panic disorder are 2%−5% and 7%−

8%, respectively.[6] In addition, it has been reported that rates of mood symptoms such as anxiety (6.3%−50.9%) and depression (14.6%−48.3%) have significantly increased since the outbreak of coronavirus disease (COVID-19).[7]

The DSM-5 presents a categorical diagnostic system that comprehensively considers the several cardinal symptoms for each psychiatric disorder, including symptoms related to mood, anxiety, cognition, perception, sleep, and energy. The DSM diagnostic system has been criticized as having various limitations, including its heterogeneity of symptoms within the same diagnosis, common coexisting psychiatric diagnoses within individuals, and clinicians' individual subjectivity can easily influence each diagnosis process.[8,9] Plus, multidimensional and integrated evaluations for diagnosis in the clinical field of psychiatry are often not properly performed, because it is difficult to separately measure numerous factors in psychiatry. Although the DSM system has separate diagnoses for mood and anxiety disorders, it is still a challenge for clinicians to differentiate such disorders in clinical settings, since mood and anxiety disorders share similar clinical symptoms across various psychiatric disorders. Therefore, a transdiagnostic approach focusing on the clinical symptoms of mood and anxiety can better reflect the actual clinical setting, rather than an approach based on the diagnosis of each mood and anxiety-related disease.

Mood and anxiety symptoms are affected by various and complex factors ranging from genetic predisposition to lifestyle, psychological distress, trauma, and environmental factors.[10-12] Therefore, the use of a multidimensional evaluation and approach considering the various causes of mood and anxiety will bring us closer to the core of the actual psychiatric symptoms. Quantification through measurement is an essential aspect of understanding a multifactorial disease. Due to this difficulty with symptom measurement, most of the psychiatric evaluations are fragmentary, localized, and discontinuous.[13] It is therefore necessary to develop a methodology that can quantitatively and continuously evaluate the psychiatric state as comprehensively as possible.

If we can collect quantitative data related to daily mood, anxiety, activity, sleep, and circadian rhythm, all of which can reflect an individual's psychiatric state, this will make it possible to broadly understand and multidimensionally evaluate each patient. This would represent a step forward in resolving the instability and ambiguity of the diagnostic system in psychiatry.[14,15] All kinds of measurable data obtained in real-time while an individual uses a digital device in daily life can be referred to as that person's digital phenotype.[16] As the spread and use of personal digital devices such as smartphones and wearable devices become universal, it will be increasingly easier to measure real-world data through various sensors and applica-

tions installed in such devices.[17] An individual's digital phenotype reflects their health-related state and can be further analyzed to cluster and predict the onset, aggravation, and relapse of psychiatric diseases in advance.[18,19]

Performing clinical research using a digital platform made it possible to conduct non-face-to-face research, which opened up the possibility of establishing and carrying out a decentralized research design.[20,21] Decentralized research design refers to new shift of clinical trials that incorporate virtual tools, such as smartphone applications, wearable devices, and sensory-based technology to not only recruit research subjects, but also acquiring trial outcomes without involving in-person contacts, which ease participants' burden in visiting a clinic or research center in a particular time like COVID-19 pandemic.[22] Decentralized research designs are suitable for investigating medical applications of new concepts such as digital therapeutics.

The Search Your Mind (S.Y.M., 心) project is designed to acquire prospective digital phenotypic data, especially on mood and anxiety symptoms such as panic symptoms, of two main subject groups: participants who visit the clinic (centralized) and online subjects who do not visit the clinic (decentralized). To maximize the advantages of the digital platform, a system that collects all possible clinical information was implemented as a smartphone app, which allowed for a centralized and decentralized research design to be planned and carried out together.

DESIGN AND METHODS

Centralized and decentralized study design

An overview of the overall study design is presented in Figure 1. The centralized research design is a combination of a general prospective observational study and a non-face-to-face study using a digital platform. This design involves face-to-face research such as informed written consent, clinical evaluation by an investigator, and blood sampling. It also includes a digital phenotype evaluation study using an application-based online platform with wearable devices given to enrolled patients. Meanwhile, the decentralized research design is a completely non-face-to-face study, the population of which consists of anonymous participants who downloaded the app and agreed to electronic informed consent forms after understanding the description of the study on the app. It also collects personalized digital phenotypic data using only an application-based online platform. The overall study was approved by the Chungnam National University Sejong Hospital Institutional Review Board (CNUSH 2020-12-016-007). Clinical Research Information Service (CRIS) approval was also obtained for conducting the study (KCT0006523). In addition,
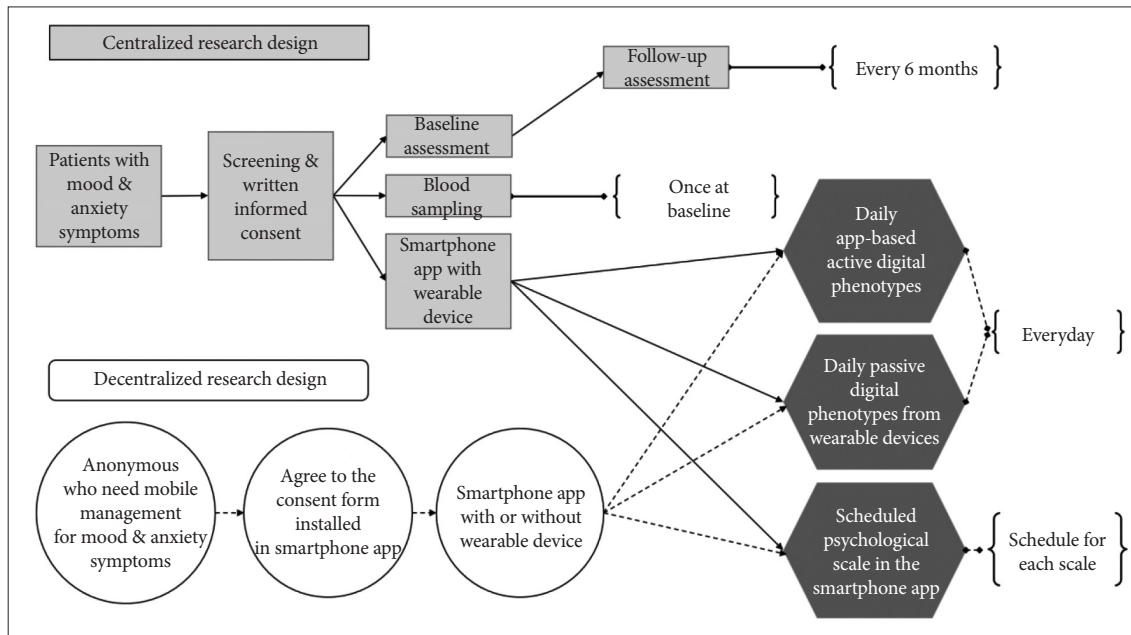
Figure 1. Schematic research flow of Search Your Mind project mixed with centralized and decentralized research design. Light gray squared figures represent the centralized research design, while white circled figures represent the decentralized research design. Dark gray hexagonal figures represent the contents of the smartphone application and wearable device used in this study, and the period and interval of the research activity are indicated in braces.

due to the characteristics of the decentralized research design, the current study is open to the possibility of multi-center research in other hospital settings, under the circumstances that an identical research process and following approval of CRIS and IRB are available.

Populations

This study is conducted by dividing the overall sample into two groups: a centralized research group (CRG) and a decentralized research group (DRG). To obtain data focusing on mood and anxiety symptoms, CRG is made up of those who were diagnosed with DSM-5 mood disorders (depressive disorder or bipolar and related disorder), anxiety disorders, trauma- and stressor-related disorders, or obsessive-compulsive and related disorders, excluding those diagnosed with intellectual disability, organic brain disease, neurocognitive disorder, or schizophrenia. Meanwhile, DRG targets those who subjectively think that smartphone app-based management for mood and anxiety is necessary. Both groups targeted adults aged 19 to 70, excluding those who do not have a smartphone. The research is carried out after providing explanations to and obtaining consent forms from for the study subjects who meet the selection criteria of this study.

Smartphone application platform with wearable devices

The smartphone application is available on both Apple's

iOS and Android OS app stores under the name "inPHRsym (Softnet Co., Ltd., Seoul, Republic of Korea)." The configuration of the app is divided into a "main menu" and an "additional menu." First, the "main menu" includes Home, Report, Diary, and Psychological scale: Home summarizes experiences of panic and emotion (mood, energy, anxiety, and irritation) over the past week. Report details the cumulative results of emotional instability, panic, lifestyle, and psychological scale. In Diary, panic (starting time, duration, symptom intensity, accompanying symptoms), emotion (mood, energy level ranging -3 to 3; anxiety, irritation level ranging 0 to 3), and lifestyle (alcohol use, caffeine, exercise, smoking, eating, menstruation) can be self-scored. Lastly, in Psychological scale, the user can complete scheduled tests recording their psychological state. The application-based psychological scales—which are inspected on monthly, quarterly, semi-annual, and yearly bases—will be covered in detail in the subsection titled "Non-face-to-face assessment for both CRG and DRG." Meanwhile, the "additional menu" includes Lifelog, Symptom encyclopedia, and Calendar. Lifelog has a sync function with wearable devices (Fitbit or Xiaomi smart band) so users can collect and check their heart rate, activity level, and sleep information using the app. Symptom encyclopedia provides information on psychiatric symptoms, according to the diagnostic criteria defined in the DSM-5. In Calendar, participants can record and check their daily emotional states using emoticons reflection states such as delight, happiness,

thrill, depression, sadness, regret, irritation, anger, and ease. Individuals can also write personal diaries about their day. The S.Y.M. app sends a pop-up notification alarm at 9 PM that suggests that the user write a Diary about the day, and an additional pop-up at 10 AM during weekends to complete the scheduled psychological scales (Table 1). The participants will either use the S.Y.M app until the end of the study or drop out of the study. A detailed app user manual can be found in the app (Supplementary Material 1 in the online-only Data Supplement).

Assessment

Face-to-face assessment for centralized research group

As shown in Figure 1, for CRG, we have conducted a baseline and follow-up psychiatric assessment, blood sampling, and digital phenotype assessment using a smartphone app paired with a wearable device. First, a follow-up assessment is performed every 6 months after the baseline assessment. In the follow-up assessment, a psychiatric evaluation is conducted using Mini International Neuropsychiatric Interview[23]

Table 1. Assessment interval of self-rating scales recorded via the smartphone app

Assessment interval (wk)	Self-rating scale
4	PHQ-9, STAI-X1, GAD-7, APPQ
12	CES-D, ACQ, BSQ, KOSS-SF, SSI, AUDIT, HSI, DAST, ILQ, SLQ, CSM, BRIAN, LES, IPAQ-SF
26	MDQ, STAI-X2, KRQ-53, WHOQOL-BREF, SWBS, KSS, TAS-20K
52	BFNE, SADS, SPAQ, DAI-10, CTQ

PHQ-9, Patient Health Questionnaire-9; STAI-X1, State-Trait Anxiety Inventory-X1; GAD-7, Generalized Anxiety Disorder Scale-7; APPQ, Albany Panic and Phobia Questionnaire; CES-D, Center for Epidemiological Studies–Depression Scale; ACQ, Agoraphobic Cognition Questionnaire; BSQ, Body Sensation Questionnaire; KOSS-SF, The Short Form of Korean Occupational Stress Scale; SSI, Beck's Scale for Suicidal Ideation; AUDIT, Alcohol Use Disorders Identification Test; HSI, Heavy Smoking Index; DAST, Drug Abuse Screening Test; ILQ, Internet Lifestyle Questionnaire; SLQ, Smartphone Lifestyle Questionnaire; CSM, Composite Scale of Morningness; BRIAN, Biological Rhythms Interview of Assessment in Neuropsychiatry; LES, Life Experiences Survey; IPAQ-SF, International Physical Activity Questionnaire–Short Form; MDQ, Mood Disorder Questionnaire; STAI-X2, State-Trait Anxiety Inventory-X2; KRQ-53, Korean Resilience Quotient-53; WHOQOL-BREF, World Health Organization Quality of Life Scale abbreviated version; SWBS, Spiritual Well-Being Scale; KSS: Korean Spirituality Scale; TAS-20K, Korean version of the 20-item Toronto Alexithymia Scale; BFNE, Brief-Fear of Negative Evaluation Scale; SADS, Social Avoidance and Distress Scale; SPAQ, Seasonal Pattern Assessment Questionnaire; DAI-10, Drug Attitude Inventory-10; CTQ, Childhood Trauma Questionnaire

along with a review of the patient's psychiatric history (coexistence of psychiatric disorder, suicide attempt history), drug treatment history (prescription drug, medication compliance, lithium administration history, and treatment response using ALDA questionnaires),[24,25] family history (mental illness or death from suicide), and clinical symptom assessment using Korean version of Montgomery Åsberg Depression Scale,[26] Young Mania Rating Scale,[27] Clinical Global Impression,[28] and Hamilton Anxiety Rating Scale.[29] The collected demographic information includes gender, age, socioeconomic status (average annual income, education level, and occupation), phone number, height, weight, marital status, number of children, religion, smoking, and medical history (past medical history, psychiatric history, recent medical history, family history, etc.). For DRG, the same evaluation items are applied in the smartphone app. CRG participants are provided with a wearable device (Fitbit HR2 or later version device) that can be worn on the participant's nondominant wrist and paired with a smartphone; wearable devices are optional for DRG. When a wearable device is linked with the app, study participants' life logs such as pulse rate, activity level, and sleep are recorded automatically.

Non-face-to-face assessment for both centralized research group and decentralized research group

The evaluation on the S.Y.M. app is conducted through both CRG and DRG, and daily panic symptoms, mood, energy, anxiety, and irritation states are scored and recorded through the application. Further, daily alcohol intake (frequency, time of the intake, type of liquor), caffeine (time of the intake, type of caffeine drink), food consumption (time of the food intake), and exercise levels (time of exercise, exercise type), smoking (number of cigarettes smoked), and menstruation status are recorded by app users. With daily data recording, light exposure is captured through an illuminance sensor in the app and automatically adjusted. The following self-reported psychological scale evaluations are also included: Patient Health Questionnaire-9,[30] State-Trait Anxiety Inventory,[31] Generalized Anxiety Disorder Scale-7,[32] Albany Panic and Phobia Questionnaire,[33] Center for Epidemiological Studies−Depression Scale,[34] Agoraphobic Cognition Questionnaire,[35] Body Sensation Questionnaire,[35] The Short Form of the Korean Occupational Stress Scale,[36] Beck's Scale for Suicidal Ideation,[37] Alcohol Use Disorders Identification Test,[38] Heavy Smoking Index,[39] Drug Abuse Screening Test,[40] Internet Lifestyle Questionnaire,[41] Smartphone Lifestyle Questionnaire,[42] Composite Scale of Morningness,[43] Seasonal Pattern Assessment Questionnaire,[44] The Korean version of the Biological Rhythms Interview of Assessment in Neuropsychiatry,[45] Life Experiences Survey,[46] The International Physical Activity Questionnaire−Short

Form,[47] Mood Disorder Questionnaire,[48] State-Trait Anxiety Inventory,[49] Korean Resilience Quotient-53,[50] Korean version of World Health Organization Quality of Life Scale abbreviated version,[51] Spiritual Well-Being Scale,[52] Korean Spirituality Scale,[53] Korean version of the 20-item Toronto Alexithymia Scale,[54] Brief-Fear of Negative Evaluation Scale,[55] Korean Social Avoidance and Distress Scale,[56] Korean Version of Drug Attitude Inventory-10,[57] and Childhood Trauma Questionnaire[58] (Table 2).

Blood sample collection
Venous blood (10 mL) is obtained at baseline for CRG only.

The blood sample is stored at ethylenediaminetetraacetic acid bottles in a -30°C freezer. It is used for genomic analysis in combination with digital and clinical phenotypic data.

Database analyses
We plan to apply various analysis methods depending on the data characteristics and hypothesis. To analyze the basic clinical data including longitudinal courses, we plan to perform paired t-test, logistic regression analysis, repeated-measures analysis of variance, Cox proportional hazard regression, mixed linear models, or other appropriate analysis methods. To comprehensively analyze the digital phenotype and clinical and

Table 2. Comparison of assessment and evaluation items used for centralized and decentralized research groups

Assessment and evaluation item	Centralized research group	Decentralized research group
Demographic information	Case report form and S.Y.M. app platform - required	S.Y.M. app platform - optional
	Gender, age, height, weight, socio-economic status, average annual household income, education level, occupation, marital status (number of children), religion, menopause (for women only)	Gender, age, height, weight, average annual household income, education level, occupation, marital status (number of children), religion, menopause (for women only)
Clinical information	Case report form and S.Y.M. app platform - required	S.Y.M. app platform - optional
	Past medical and psychiatric history, current medication history, previous suicide attempt history, current suicidal ideation and attempt, family history, smoking, alcohol drinking	Past medical and psychiatric history, current medication history, previous suicide attempt history, current suicidal ideation and attempt, family history
Blood sample collection	Venous blood 10 mL	-
Objective assessment (by clinical investigator)	MINI, ALDA, MADRS, YMRS, CGI-BP, HAM-A	-
Subjective assessment (self-rating)	S.Y.M. app platform - required	S.Y.M. app platform - optional
	PHQ-9, STAI-X1 and X2, GAD-7, APPQ, CES-D, ACQ, BSQ, KOSS-SF, SSI, AUDIT, HSI, DAST, ILQ, SLQ, CSM, SPAQ, BRIAN, LES, IPAQ-SF, MDQ, KRQ-53, WHOQOL-BREF, SWBS, KSS, TAS-20K, BFNE, SADS, DAI-10, CTQ	
S.Y.M. app platform		
Daily Lifelog	Alcohol, caffeine, smoking, meal, exercise, menstruation (for women only)	
Daily Mood Log	Panic symptoms (onset time, duration, intensity, detailed symptom type)	
	Affective states (mood, energy, anxiety, irritation) scoring	
Mood Calendar	Today's mood (emoticon), stories about today (freewriting)	
Wearable device	Fitbit wearables - required	Fitbit or Xiaomi wearables - optional
	Heart rate, activity, sleep	Heart rate, activity, sleep

S.Y.M. app, Search Your Mind application; MINI, Mini International Neuropsychiatric Interview; ALDA, ALDA questionnaire for Lithium treatment response; MADRS, Montgomery Åsberg Depression Scale; YMRS, Young Mania Rating Scale; HAM-A, Hamilton Anxiety Rating Scale; CGI-BP, Clinical Global Impression-Bipolar; PHQ-9, Patient Health Questionnaire-9; STAI, State-Trait Anxiety Inventory; GAD-7, Generalized Anxiety Disorder Scale-7; APPQ, Albany Panic and Phobia Questionnaire; CES-D, Center for Epidemiological Studies–Depression Scale; ACQ, Agoraphobic Cognition Questionnaire; BSQ, Body Sensation Questionnaire; KOSS-SF, The Short Form of Korean Occupational Stress Scale; SSI, Beck's Scale for Suicidal Ideation; AUDIT, Alcohol Use Disorders Identification Test; HSI, Heavy Smoking Index; DAST, Drug Abuse Screening Test; ILQ, Internet Lifestyle Questionnaire; SLQ, Smartphone Lifestyle Questionnaire; CSM, Composite Scale of Morningness; SPAQ, Seasonal Pattern Assessment Questionnaire; BRIAN, Biological Rhythms Interview of Assessment in Neuropsychiatry; LES, Life Experiences Survey; IPAQ-SF, International Physical Activity Questionnaire–Short Form; MDQ, Mood Disorder Questionnaire; KRQ-53, Korean Resilience Quotient-53; WHOQOL-BREF, World Health Organization Quality of Life Scale abbreviated version; SWBS, Spiritual Well-Being Scale; KSS, Korean Spirituality Scale; TAS-20K, Korean version of the 20-item Toronto Alexithymia Scale; BFNE, Brief-Fear of Negative Evaluation Scale; SADS, Social Avoidance and Distress Scale; DAI-10, Drug Attitude Inventory-10; CTQ, Childhood Trauma Questionnaire

genomic data of the individuals, analysis methods such as machine learning will be actively used. The following data will be used to predict specific clinical events, including panic attacks and relapse risk of mood or anxiety episodes. In addition, it can also be used to identify any new subphenotype of a psychiatric disorder, which can be utilized for understanding and reconstructing diagnosis criteria.

CONCLUSION

To date, most clinical research in psychiatry has mainly involved a conventional centralized research design. In this study protocol, we explain the design and methods of a prospective smartphone app-based study for the digital phenotyping of mood and anxiety symptoms mixed with centralized and decentralized research forms. In this project, we can collect digital phenotypes by measuring daily mood and anxiety states with life logs using wearable devices and the S.Y.M. application. Through the systematic and harmonious collection of patients' clinical, biological, and digital data, this study is expected to open up opportunities for the development of personalized psychiatry approaches that can predict each person's psychiatric condition and thus provide tailored treatment options. By maximizing and applying digital technology, our study presents the possibility of realizing a mixed model of centralized and decentralized research design for use in future studies.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.30773/pi.2022.0102.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Chul-Hyun Cho. Writing—original draft: all authors. Writing—review & editing: all authors.

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