Review

Digital Sensory Phenotyping for Psychiatric Disorders

Jiacheng Dai [1], Yu Chen [1], Cuihua Xia [1], Jiaqi Zhou [1], Chunyu Liu [1,2,*], Chao Chen [1,3,*]

[1] Center for Medical Genetics & Hunan Key Laboratory of Medical Genetics, School of Life Sciences, Central South University, Changsha 410000, China
[2] Department of Psychiatry, SUNY Upstate Medical University, Syracuse, NY 13210, USA
[3] National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha 410000, China
* Correspondence: Chunyu Liu, Email: liuch@upstate.edu; Chao Chen, Email: chenchao@sklmg.edu.cn.

ABSTRACT

Today's genome-wide association studies (GWAS) of psychiatric disorders require massive sample sizes and the identification of biologically relevant phenotypes. Sensory phenotypes, assessed by measuring sensorial function, represent early symptoms of psychiatric disorders, and may involve neurobiological pathways in psychiatric disorders. Yet, sensory phenotypes have rarely been studied in large populations for early diagnosis or GWAS. The concept of using digital devices to collect data on disease-related phenotypes is beginning to attract considerable attention. Is it possible to assess sensory phenotypes dynamically by digital devices? And furthermore, is it possible to explain the pathology of psychiatric disorders through those assessments? In this review, we summarize studies investigating sensory phenotypes and digital phenotyping of psychiatric disorders. We discuss the feasibility of digital phenotyping to better capture disease-related sensory phenotypes. We also discussed potential ethical and privacy issues, which require regulation of governments and collaborations of all researchers to solve. While the emergence of digital phenotyping makes the large-scale and moment-by-moment quantification of sensory phenotypes in psychiatric disorders highly scalable, it also introduces tremendous opportunities for genetic research and health improvement.

KEYWORDS: psychiatric; phenotype; sensory phenotype; digital phenotyping

Open Access

Received: 30 December 2019
Accepted: 24 June 2020
Published: 28 June 2020

Copyright © 2020 by the author(s). Licensee Hapres, London, United Kingdom. This is an open access article distributed under the terms and conditions of Creative Commons Attribution 4.0 International License.

INTRODUCTION

Sensory phenotypes are the sum of complex traits that reflect the

function of the human senses (seeing, hearing, smelling, tasting, and touching) responding to environmental stimuli. Accumulating evidence suggests that sensory defects represent the earliest symptoms of most psychiatric disorders [1–4]. As disease symptoms, sensory phenotypes may help clinical diagnosis and treatment through earlier detection of disease onset, relapse and improvement. Labeled as an endophenotype (having genetically-associated, predictable behavioral symptoms), sensory phenotypes may share some neurophysiological pathways common to psychiatric disorders; additionally, sensory phenotypes may also act as a direct index for neurophysiological effect [1]. Researchers have used sensory phenotypes to identify specific genotypes and to explain psychiatric disorders [5]. However, the existing low-throughput, high-cost methods for measuring sensory phenotypes are also impractical. They are not easily integrated into the massive data sets used in today's genome-wide association studies (GWAS). Therefore, applying convenient and high-throughput digital technologies to measure sensory phenotypes carries great potential for studying psychiatric genetics.

Sensory phenotypes that measured with digital technologies are defined as digital sensory phenotypes. Using common digital technologies such as smartphones and wearable devices to measure and collect personal phenotypic data, termed "digital phenotyping" has tremendous potential [6–8]. Today, researchers are collecting phenotypic data from patients with psychiatric disorders including such parameters as daily mood, physical activities, and social communications using relatively inexpensive digital devices [9,10]. Digital phenotyping is unobtrusive—even a normal smartphone can capture many types of phenotypic data. In psychiatry, objective and continuous quantitation of clinical markers using patients' own devices is useful to refine diagnosis, to tailor treatment strategy or monitor outcomes [11]. Through digital phenotyping, we can capture behavioral and sensor changes, and self-report information. These changes should be distinguishable in nature and clinical status, and detectable by smartphone, wearable devices or other sensors. Among lots of human phenotypes, sensory phenotypes are eligible for the requirements.

In this review, we summarize studies that correlate sensory phenotypes to psychiatric disorders and those that use digital technologies to collect phenotypic data from patients with these psychiatric disorders. We consider both sensory (perceptual) and sensorimotor functions as identifying sensory phenotypes. Sensorial functions refer to the basic abilities of sensory receptors and related neural circuitries, whereas sensorimotor functions refer to both sensory inputs and motor responses, e.g., eye movement or auditory EEG [12]. Abnormalities in sensory or sensorimotor functions suggest defects in the integrity of neural pathways and the nervous system as a whole [13]. Perception involves somewhat

complex subjective judgment and is difficult to measure; therefore, we restricted our discussion in this essay to sensorimotor functions. Involving only limited little cognitive function, sensorimotor functions reflect sensory circuits directly. We are particularly interested in the feasibility of collecting sensory phenotypic data via digital technology and correlating those phenotypes to genetic variants associated with psychiatric disorders (see Figure 1).

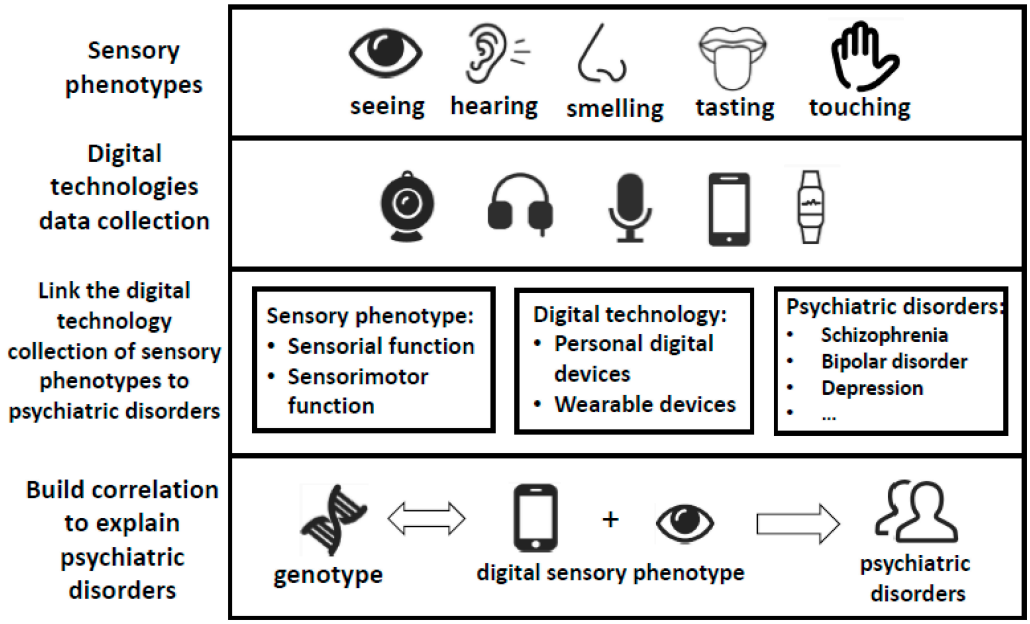

Figure 1. Overview: In this review, we introduce the concepts of the sensory phenotype and digital phenotyping for psychiatric studies. Furthermore, we discuss the feasibility of using digital technology to collect sensory phenotypes of psychiatric disorders.

PHENOTYPES IN PSYCHIATRIC GENETIC STUDIES

Diagnosis serves as a categorical phenotype for GWAS [1]; yet, diagnostic validity depends on how diagnosis is defined and whether its criteria are logically and factually reasonable [14–16]. For example, the clinical definition of autism has changed remarkably over the past 75 years. Once thought to be a form of childhood schizophrenia, autism is now considered a neurodevelopment disorder with genetic origins. Diagnoses such as these are conventionally not based on expert observation and objective assessment and not on the physiological etiology [17,18]. Psychiatric disorders are difficult to classify due to their multidimensional phenotypes [16]. This difficulty is compounded by the burden of imprecise phenotyping, which impedes the identification of risk genes that contribute to psychiatric disease susceptibility [19].

The use of endophenotypes is one proposed method for linking disease diagnosis to genetic risk variant detection [20]. Endophenotypes are heritable, objective biological markers that can be measured directly.

Endophenotypes may be categorized as neurophysiological, endocrinological, neuroanatomical, or cognitive [20]. Because they are directly measured and quantifiable, endophenotypes may be superior to traditional methods of diagnoses [20,21]. For example, sensory motor-gating deficits consistently characterize schizophrenia [22–24]. Compared to complex disease behaviors, endophenotypes are governed by fewer genes. These genes may play an important role in the disease. Endophenotypes may bridge disease diagnosis and gene identification, identifying "downstream" clinical phenotype traits as well as "up-stream" genetic output [20]. Endophenotypes may also help to identify aberrant genes in polygenic disease [25]. Furthermore, patients may be subclassified by specific endophenotypes [1]. Multiple endophenotypes could work together to constitute subtypes of the current diagnosis. The biology of endophenotypes contribute a fundamental understanding of the disease process, which has the potential to assist in prevention and more effective treatments [26].

Using endophenotypes offers a quantifiable method for diagnosis. This is plausibly a more precise and reproducible method than the qualitative, subjective categories of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Furthermore, as a straightforward biological construct, endophenotypes are likely more accurate than conventional means in pinpointing a specific genetic abnormality and corresponding protein change [23]. Nonetheless, developing a truly high-grade and accurate endophenotype is a critical challenge. Researchers have identified and validated potential endophenotypes typically from disease-linked deficits [27]. Evidence of segregation and heritability in "clinically unaffected" relatives is a genotype-endophenotype correlation that commonly used for individual pedigree members [27]. For example, P50 suppression deficits were found as potential endophenotypes in patients with schizophrenia and unaffected relatives [28], which has been widely replicated and confirmed [26,29–33]. Additionally, an association study identified the chromosomal region of interest [34], which yielded an association of P50 suppression deficits in schizophrenia via the α-7 subunit of the nicotinic receptor [35]. P50 suppression is considered to be one endophenotype of schizophrenia.

Several consortiums are attempting to apply multiple endophenotypes to large samples of patients [36]. Success will attest to the feasibility of endphenotypes for diagnosis within genetic studies [37]. The National Institute of Mental Health initiated the Research Domain Criteria (RDoC) project in 2009 [14]. RDoC focuses on psychological systems including emotion, cognition, motivation, and social behavior, as well as the specific system's relationship to mental health and illness in general. The Bipolar Schizophrenia Network on Intermediate Phenotypes (BSNIP) project, adherent to RDoC guidelines, aims to systematically investigate

phenotypic components of schizophrenia (SCZ) and bipolar disorder (BD) [38]. BSNIP measures physiological or cognitive traits, such as electroencephalography (EEG), eye movement activity and brain imaging. Likewise, the Enhancing Neuroimaging and Genetics through Meta-Analysis (ENIGMA) Network uses advanced imaging technology to collect complex phenotyping data, identifying genetic influences on brain structure and function [39].

SENSORY PHENOTYPES IN PSYCHIATRIC DISORDERS

Sensory phenotypes are one of endophenotypes for psychiatric disorders. As the technology for collecting sensory measurements improves, interest among mental health professionals is growing. Researchers can now capture previously undetectable sensory phenotypes and test various proposed phenotypes for their correlation to psychiatric characteristics. For example, deficits in the sense of smell are a sensory phenotype linked to negative symptoms in patients with schizophrenia [40]. One meta-analysis showed a deficient sense of smell in patients with schizophrenia and at-risk youth [41]. Wheras, patients with autism spectrum disorder (ASD) show heightened sensorimotor function. ASD prompts atypical sensory reactivity and sensory over-responsivity [42,43], characterized by an extremely negative response to sensory stimuli [44]. ASD's sensory over-responsivity correlates to abnormal changes in the connectivity between the thalamus and the cortex [45]. Furthermore, eye-tracking deficiency in schizophrenia has also been investigated [46]. Chronic pain can be an example of a tactile phenotype of the whole body that is associated with anxiety and depression within epidemiological studies. Individuals with major depressive disorder (MDD) and other psychiatric disorders have an increased risk for chronic pain [47]. Recent research points to overlaps between pain- and depression-related changes in neuroplasticity and neurobiological mechanisms [48]. The sensory pathway of physical pain may involve multiple brain regions, including the insular and prefrontal cortices, associated with mood management [49].

To review the sensory phenotype study in psychiatric disorder, we searched studies of sensory phenotypes in psychiatric disorders in PubMed with the following search builder: (((((((visual) OR olfactory) OR auditory) OR tactile) OR gustatory) OR sensory phenotype)) AND (#DISORDER#). #DISORDER# is one of the major psychiatric disorders: SCZ, BD, MDD, anxiety, obsessive-compulsive disorder (OCD), Alzheimer's disease (AD) and Huntington's disease (HD). We also used the following inclusion criteria: (1) published in English before March 2018; (2) assessed sensory phenotype in at least one of the psychiatric disorders; and (3) case-control studies only. We chose 55 articles for the following tabulation.

In total, we selected 55 case-control studies, involving sensory

phenotype of seven psychiatric disorders, including SCZ, BD, MDD, anxiety, OCD, AD, and HD. Significant differences between the disease and control populations were detected in case-control studies for several sensory phenotypes, e.g., eye-tracking in SCZ, BD, and MDD [50]; auditory event-related potential [51–53] in SCZ, BD, and anxiety; phenylthiocarbamide (PTC) non-taste in SCZ [54,55]; olfactory identification ability in SCZ [56] and AD [57]; and, tactile phenotype in OCD [58]. These studies focused primarily on differences in sensory phenotypes between patients with specific psychiatric disorders and healthy controls; they also reflect an interest in investigating the biological correlates of sensory function and psychiatric disorders. Tabulating the sample size and P-values of sensory phenotypic studies, researchers found that sensory phenotypes do significantly correlate with psychiatric disorders (Table 1). However, sample sizes were relatively small. In fact, most case-control studies had sample sizes under 400, with only two studies that used EEG measurements which included over 1000 participants. Sensory phenotypes are widely studied in the field of psychiatric disorders, however, mostly with small sample sizes.

In genetic studies, sensory phenotype research showed evidence of their correlation to psychiatric disorders. The fact that sensory phentopyes assist in detecting the genetic loci of psychiatric risks also attracts much attention [1]. One GWAS found that the sense of smell shares genetic regions with schizophrenia and Alzheimer's disease on chromosome 18 (see Table 2). [103] They identified olfactory-related genetic regions using 8561 samples from the Religious Orders Study and Memory and Aging Project (ROSMAP), the Atherosclerosis Risk in Communities (ARIC) and the Health, Aging, and Body Composition (Health ABC) studies [103,104]. The same GWAS identified genetic loci associated with sensory phenotypes previously linked to schizophrenia [103]. One GWAS studying eye movement detected genomic regions also shared with schizophrenia risk loci [105]. Another GWAS of eye movement dysfunction in 128 schizophrenia patients also confirmed schizophrenia-related abnormalities in eye movement tasks. Additionally, 5 SNPs in MAN2A1 were significantly associated with cognitive search scores [106] that estimate the frequency of eyes focusing on the important areas within a figure [107].

Table 1. Summary of sensory phenotypic studies in psychiatric disorders.

Disease	Sensory type	Phenotype	Phenotype measurement	Total sample	*p*	Reference
AD	Olfactory	Olfactory identification ability	UPSIT	68	0.001	Doty1987 [57]
Anxiety	Auditory	P300 (positive deflection) event-related potential	EEG recording	256	0.0004	Enoch2008 [53]
Anxiety	Auditory	Brain responses to musical	fMRI and music stimuli	26	0.01	Thornton-Wells2010 [59]
BD	Auditory	Event-related potential	Electrophysiological recording	545	no.sig	Bertelsen2015 [60]
SCZ and BD	Auditory	P50 evoked potential	Electrophysiological recording	222	0.001	Cabranes2013 [61]
BD	Auditory	Event-related potential amplitudes during auditory oddball task	EEG recording	1204	0.001	Ethridge2015 [52]
BD	Visual	Eye-tracking	Control of attention test	48	0.001	García-Blanco2017 [62]
BD	Auditory	P50 evoked potential	EEG recording	167	0.01	Hall2008 [63]
BD	Auditory	EEG evoked time-voltage/time-frequency domain	EEG recording	1120	0.05	Hamm2014 [64]
Huntington's disease	Olfactory	Olfactory identification ability	UPSIT	60	0.001	Bylsma1997 [65]
OCD	Tactile	Simple reaction time, choice reaction time, dynamic (detection) threshold, amplitude discrimination, and amplitude discrimination with single-site adaptation	Psychophysical experiments	64	0.001	Güçlü2015 [58]
SCZ	Auditory	MEG recording	MEG	42	no.sig	Bachmann2010 [66]
SCZ	Visual	Eye-tracking	Eye-tracking system	50	0.02	Bortolon2016 [67]
SCZ	Olfactory	Olfactory identification ability	UPSIT	112	0.005	Brewer2003 [56]

Table 1. *Cont.*

Disease	Sensory type	Phenotype	Phenotype measurement	Total sample	*p*	Reference
SCZ	Gustatory (tasting)	PTC non-taste	PTC taste	272	no.sig	Brewer2012 [68]
SCZ	Auditory	P50 and N100 Amplitudes	Electroencephalogram	151	0.002	Brockhausdumke2008 [69]
SCZ	Auditory	P50 evoked potential	Electrophysiological recording	248	0.001	Cabranes2013 [61]
SCZ	Gustatory	PTC non-taste	PTC taste	93	0.001	Compton2013 [55]
SCZ	Olfactory	Cerebral blood flow response to olfactory task	Positron emission tomographic study	34	0.03	Crespo-Facorro2001 [70]
SCZ	Auditory	P50 evoked potential	EEG recording	46	0.005	Erwin1998 [71]
SCZ	Auditory	Event-related potential amplitudes during auditory oddball task	EEG recording	1204	0.001	Ethridge2015 [52]
SCZ	Auditory	EEG evoked time-voltage/time-frequency domain	EEG recording	1120	0.05	Hamm2014 [64]
SCZ	Auditory	P50 evoked electroencephalographic response	EEG recording	57	0.03	Hazlett2015 [72]
SCZ	Auditory	Event-related potentials (two-tone passive auditory oddball paradigm)	EEG recording	34	0.01	Hermens2010 [73]
SCZ	Auditory	P50 evoked potential	EEG recording	60	0.0001	Kéri2010 [74]
SCZ	Olfactory	Olfactory identification ability	UPSIT	24	0.05	Kopala1998 [75]
SCZ	Olfactory	Olfactory identification ability	UPSIT	89	0.04	Kopala2001 [76]
SCZ	Gustatory and olfactory	Sniffin' Sticks smell and taste strips for taste testing	The Sniffin’ Sticks test	52	0.034	Lang2011 [77]
SCZ	Auditory	Mismatch negativity and P3a amplitudes	EEG recording	1790	0.001	Light2015 [78]

Table 1. *Cont.*

Disease	Sensory type	Phenotype	Phenotype measurement	Total sample	*p*	Reference
SCZ	Olfactory	Olfactory identification ability	Smell Identification Test	67	0.02	Malaspina2002 [79]
SCZ	Auditory	P50 evoked potential	Electrophysiological Recording	186	0.001	Martin2007 [80]
SCZ	Olfactory	Olfactory identification ability	Suprathreshold Amyl Acetate Odor Intensity and Odor Pleasantness Rating Test	60	0.001	Moberg2003 [81]
SCZ	Gustatory	PTC non-taste	PTC taste	77	0.02	Moberg2005 [82]
SCZ	Olfactory	Olfactory identification ability	PTC taste	41	0.026	Moberg2006(a) [83]
SCZ	Olfactory	Olfactory identification ability	UPSIT	54	no.sig	Moberg2006(b) [84]
SCZ	Gustatory	PTC non-taste	PTC taste	127	0.002	Moberg2007 [85]
SCZ	Gustatory	PTC non-taste	PTC taste	405	0.02	Moberg2012 [54]
SCZ	Auditory	P50 evoked potential	EEG recording	126	0.001	Myles-Worsley2004 [86]
SCZ	Visual	Visual scan	Measurements of visual scan paths	24	0.05	Phillips1997 [87]
SCZ	Olfactory	Regional cerebral blood flows	The H2(15)O-PET technique	24	0.05	Plailly2006 [88]
SCZ	Auditory	P50 suppression	EEG recording	1821	0.0002	Quednow2012 [51]
SCZ	Olfactory	Olfactory identification ability in both nostrils	Unirhinal (in one nostril) odor identification and detection threshold sensitivity tests	95	0.04	Roalf2006 [89]

Table 1. *Cont.*

Disease	Sensory type	Phenotype	Phenotype measurement	Total sample	*p*	Reference
SCZ	Visual	Eye-tracking	A nonverbal intention attribution task, eye movements record	58	0.001	Roux2016 [90]
SCZ	Olfactory	Olfactory identification ability	The Sniffin' Sticks test	73	0.001	Rupp2005 [91]
SCZ	Olfactory	Brain activation (fMRI)	Mood induction and functional magnetic resonance imaging	52	0.05	Schneider2007 [92]
SCZ	Auditory	P50 event related potential	EEG and MEG recording	20	no.sig	Thoma2005 [93]
SCZ	Auditory	Early auditory information processing	Early auditory information processing	1415	0.001	Thomas2017 [94]
SCZ	Olfactory	Olfactory bulb volume	MRI	48	no.sig	Turetsky2000 [95]
SCZ	Olfactory	Olfactory identification ability	Olfactory stimulation and OERP record	41	0.044	Turetsky2003(a) [96]
SCZ	Olfactory	Olfactory bulb volume	Olfactory threshold detection sensitivity and identification test scores	90	0.05	Turetsky2003(b) [97]
SCZ	Olfactory	Olfactory bulb volume	MRI	50	0.05	Turetsky2003(c) [98]
SCZ	Olfactory	Olfactory neuron response	Hydrogen sulfide stimuli	39	0.05	Turetsky2009 [99]
SCZ (First-episode)	Olfactory	Olfactory identification ability	UPSIT	112	0.001	Brewer2001 [40]
SCZ (Monozygotic twins)	Olfactory	Sniffin' Sticks olfactory identification ability	The Sniffin' Sticks test	20	0.01	Ugur2004 [100]

Table 1. *Cont.*

Disease	Sensory type	Phenotype	Phenotype measurement	Total sample	*p*	Reference
SCZ and TLE	Olfactory	Odor identification ability and detection threshold sensitivity	UPSIT	97	0.008	Kohler2001 [101]
SCZ and paranoia	Auditory	P50 amplitudes	Electrode recording	46	0.006	Boutros1993 [102]
SCZ, BD and MDD	Visual	Visual contrast, visual motion integration	Motion detection task	249	0.05	Carter2017 [50]
SCZ, BD and MDD	Auditory	Auditory tone and auditory tone integration	Auditory integration and response task	249	0.01	Carter2017 [50]

Abbreviations: Electroencephalogram, EEG; event-related potential, ERP; magnetoencephalography, MEG; Magnetic Resonance Imaging, MRI; phenylthiocarbamide, PTC; temporal lobe epilepsy, TLE; significant *p*-value in the article, *p*; University of Pennsylvania Smell Identification Test, UPSIT.

Table 2. Genetically overlapped GWAS regions related to the sense of smell in schizophrenia (SCZ), and major depressive disorder (MDD).

Phenotype	variant	Chromosome	Start position	End position	Reference
Sense of smell	rs115661734	18	52,889,562	53,804,767	Dong2017 [103]
MD	rs149735550	18	52,866,733	53,440,658	Arnau-Soler2019 [108]
SCZ	chr18_52749216_D	18	52,747,686	52,752,696	PGC2014 [109]
SCZ	rs78322266	18	52,987,176	53,172,676	PGC2014 [109]

Technology for measuring sensory phenotypes has developed at a slower pace than DNA sequencing technology. While the cost of DNA sequencing has declined, throughput has increased significantly. DNA extracted from saliva or blood is effective, and sequencing provides coverage of the entire genome. Conversely, aspects of mental health phenotypic measurements such as cost, throughput and some others are lagging compared with the progress made in sequencing technology, for instnace. Furthermore, measurement systems are generally inconvenient. The University of Pennsylvania Smell Identification Test (UPSIT) has been used as a gold standard for olfactory sensorial function. Although the method is reliable [110] and practical, researchers are determined to improve its accuracy and convenience [111]. Likewise, measurement systems also are often time-consuming and inaccurate. The auditory event-related potential (ERP) is used to collect auditory phenotypes [52,53,64], measuring brain response related to sensory, cognitive, and motor events [112]. We found that the most frequently used measurement for hearing is the electroencephalogram (EEG) recording of the P50 and P300 waves [113]. Meanwhile, an EEG test requires up to 60 min of a participant's time, while participants wear a snug electrode cap which must be fitted correctly. Although a smaller, portable EEG has been developed, ambient noise in an uncontrolled environment can be problematic, rendering false test results [114]. Even though ERP is one of the most widely used methods in cognitive neuroscience, the procedures are often complicated and inefficient. Eye movement has been the dominant test for the visual sensorimotor function to date [50,62,67,90]; however, it is another low-throughput method and lacks a unified standard for quality control. The digital recording represented by ERP and eye movement fill the gap of collecting complex phenotype, but the cost of digital recording measurements is still high due to specialized devices and the need for professional operation. In order to collect sensory phenotypes for a conventional study using large populations, high-throughput measurements are required. Embracing the handheld digital technology revolution will allow researchers to generate adequate data needed to establish definitive sensory phenotypes.

DIGITAL PHENOTYPING AS A DEVELOPING PHENOTYPE MEASUREMENT

Digital phenotyping is a method for measuring phenotypes that uses digital technology such as smartphones and wearable devices and allows for a continuous collection of clinical data [115]. As personal technology becomes increasingly embedded in modern society, the possibilities for digital phenotyping have flourished. Patients with psychiatric disorders increasingly own smartphones that could be used to benefit their health [116]. Researchers could collect patient's phenotypic data from smartphone sensors and wearable devices to determine health status [117].

Digital phenotyping encompasses the collection of data for symptoms relevant to psychiatric disorders as either passive or active data. "Passive data" refers to data produced with the patient's approval but without the patient having to iniatiate a response; these include GPS and accelerometer data collected by smartphones automatically [8]. Another digital phenotype analysis strategy is the ecological momentary assessment (EMA) [118,119] that uses "active data". "Active data" requires not only the patient's approval but also the patient's active involvement, such as taking surveys or contributing audio samples [8]. For instance. using a smartphone application, patients can keep an accurate diary of their symptoms and behaviors [120].

In the last 5 years, smartphone applications for monitoring psychiatric disorders have proven feasible. We searched studies of digital phenotyping in psychiatric disorders in PubMed with the following search builder: ((((((schizophrenia) OR bipolar disorder) OR major depression disorder) OR suicide) OR neuropsychiatric)) AND (((digital phenotyping) OR smartphone) OR wearable devices). Inclusion criteria contained the following: (1) Published in English before December 2019; (2) Applying digital phenotyping in at least one of the psychiatric disorders; and, (3) Case-control study only. We found digital phenotyping studies of MDD [121–124], BD [125,126], SCZ [120,127–130] and other disorders [131–134]. For example, with the Beiwe smartphone platform [135], Barnett et al. [127] used mobility patterns and social behavior to predict relapse in schizophrenia. They found that the rate of behavioral anomalies was 71% higher within the two weeks preceding relapse. Saeb et al. [123] collected 48 college students' location sensor data and evaluated their depression symptoms severity using Patient Health Questionnaire 9-item (PHQ-9). They found several digital phenotyping measures significantly correlated with PHQ-9 scores (p-values < 0.05). Beiwinkel et al. [125] monitored social information to track daily mood, physical activity, and social communications in 13 patients with bipolar affective disorder, finding that changes in symptom levels correlated to the smartphone measures. These researchers characterized digital phenotyping as a practical tool for psychiatric-related phenotypic measurement. Their studies reinforce that

the technology revolution and information science can support the field of mental health. Many of these studies tried to prove that digital phenotyping is eligible in routine clinical practice by enhancing clinical diagnosis and treatment through monitering earlier signs of disease onset, relapse or treatment response. However, practical feasibility is one important consideration. We think that sensory phenotype might be one of the feasible choice.

USING DIGITAL PHENOTYPING TECHNOLOGIES TO CAPTURE AND ANALYZE SENSORY PHENOTYPES

The range of available sensor input methods is wide and varied. Taps, clicks, scrolls, and cameras, with human-device interaction information provide multiple measures of sensory function. In regard to tactile phenotype, individuals with OCD, for example, can have abnormal touching patterns captured by a touchscreen [58,77]. For visual phenotypes, individuals with BD may possess inefficient eye-tracking and visual contrast sensitivity [50], which can be captured by a smartphone camera. Improved resolution and refresh frequency of phone cameras will allow the capture of increasingly complex traits related to eye movements that can currently only be analyzed using special devices [136,137]. With regard to auditory phenotypes, it is well known that individuals with BD and MDD can experience auditory verbal hallucinations in response to auditory stimuli. This can be measured by combining the capture of validated auditory stimuli through earphones and the user's interpretation documented on touchscreen [138]. Quality earphones and advanced audial technology can make studies related to sensitivity and the ability to differentiate direction and tone possible. In terms of smelling, tasting, and tactile phenotypes, individuals with SCZ often lose their ability to distinguish some smells and tastes [76]. While no sensors for measuring smell or taste-related phenotypes exist to date, patient-reporting of symptoms documented through smartphones could provide meaningful data.

The digital measurement of sensory functions represents a powerful tool for capturing a host of sensory phenotypes. Eye tracking can be used to refine diagnostic process or to monitor early signs of disease relapse, but it has yet to become a pervasive technology. Researchers used convolutional neural network to build the eye tracking software that work on commodity hardware such as mobile phones and tablets, without the need for additional sensors or devices. For example, Krafka et al. trained a convolutional neural network for eye tracking, reducing error rate over previous approaches while running on a modern mobile device [139]. This algorithm had been applied to study of ASD patients. Strobl et al. assessed the accuracy of distinguishing between gaze towards the eyes and the mouth with smartphone, providing opportunities for more quantitative

monitoring of ASD patients [140]. Lai et al. also used a deep convolutional neural network, resulting in negligible differences between a smartphone and a high-speed camera in saccade latency, an eye movement measure of reaction time [141]. Comparing to eye tracking measurement, hearing test via smartphone may be easier. Using a smartphone app, Teki et al. evaluated auditory issues by segregating dialogue from background noise, known as the "cocktail party problem" [142]. The researchers evaluated participants' ability to detect complex figures dictated by multiple voice frequencies against a noisy background. Results highlighted the potential use of smartphone apps in capturing robust large-scale auditory behavioral data from normal healthy volunteers and clinical populations. De Sousa et al. reported a smartphone digits-in-noise hearing test of 24,072 persons in South Africa [143]. Their study indicated that such a hearing test app can address a public health need. However, hearing test using smartphone also have some technical limitations. For example, different type of earphone transducer will influence the accuracy of hearing test [144].

These researchers proved that digital biomarkers can be correlated to gold-standard neurocognitive tests using passively acquired data during daily smartphone use. Digital technology can detect sensory phenotypes in an unobtrusive and economical way, providing data-rich daily assessments of sensory functions and continuous feedback for clinical intervention. To date, the application of digital technology to measure sensory phenotypes was relatively limited, yet this could change in the future. Phenome-wide association studies (PheWAS) could involve a large spectrum of phenotypes captured by digital technologies, useful in pleiotropic genetic associations. Compared with the conventional GWAS design, PheWAS examines a limited set of target genotypes and their association with multiple phenotypes [145,146]. Similar to electronic health records (EHR), digital technologies can also provide a longitudinal and comprehensive phenotypic record of sensory phenotype [147].

Privacy and data security are vital factors that must be considered with the use of digital sensory phenotyping [148,149]. New technologies enlarging upon the meaning of "personal data" necessitate more rigorous data safety and greater privacy protection. It is critical that smartphones do not collect personal data without patients clear understanding what this permission entails compliant with the regulations for patient's rights specific to the country of origin. While researchers may make use of anonymous digital sensory data, maintaining the anonymity of smartphone data is tremendously challenging. Barnett et al. constructed a software platform designed to support the conduct of digital phenotyping for research studies [150]. They protect data using privacy-preserving mechanisms designed to collect only anonymized participant data by default. Their design proves that anonymizing digital data collected on

smartphones is possible. Researchers who study digital sensory phenotype must follow all privacy guidelines established for medical research, including respect for autonomy, beneficence, nonmaleficence, and justice [151]. Unfortunately, inadequate privacy protection has already infested digital health care collections, including estimations of mental health and behavior, as discovered by a 6-month systematic assessment [152]. Privacy issues have often been too narrowly focused, with too few authentications and privacy protocols in place [148]. Only completely up-to-date privacy assessments are likely to uncover these evolving problems. Further attention will be required to ensure that digital health care privacy is adequate.

While smartphones and the Internet may solve specific problems in psychiatry, their clinical use raises new ethical challenges that the collective global society should endeavor to solve. Similar concerns have been raised in other fields. For example, Wand et al. discovered that deep neural network analysis of facial images may threaten the privacy and safety of gay men and women [153]. To solve the problem, Martinez-Martin et al. emphasized that ethical, legal and social implications of digital technology must be addressed. Existing ethical and regulatory frameworks for the provision of mental healthcare clearly do not apply to this field [154]. The authors address transparency, informed consent, privacy, and accountability, aspects that must also require careful consideration in the development of digital sensory phenotype data collection strategies. Shah suggests that smart privacy regulations by governments would be the most effective approach for restricting inappropriate use of personal data [155]. Similarly, the European Union implemented the General Data Protection Regulation, providing those nations with a legal framework to follow should data breaches occur [155]. This regulation might be a starting point for the development of similar regulatory processes for digital sensory phenotype data collection. For academia, it is essential to remember that collecting clinical data on human subjects requires adherence to globally accepted ethical regulations. They require scientific proof and the free volition of participants. Meanwhile, we should also seek ways to make such data generally available. Similar to John Sulston's advocacy that data from the Human Genome Project is openly accessible to the scientific community for common good, researchers should work to ensure that sensory phenotype data are used only for the common good [155].

CONCLUSION AND FUTURE DIRECTION

Digital technology can increase throughput and reduce the cost of measuring human sensory phenotypes. At the same time, digital technology has the potential to capture digital sensory phenotypes in large-scale populations of large genotypic data, such as GWAS. It has been

said that “new directions in science are launched by new tools much more often than by new concepts” [156]. Meanwhile, new measurement technologies can produce new types of data, analysis platforms, data storage, and protection strategies. Likewise, new technologies elicit new security, privacy, and ethical problems that beg adequate resolution. Advances in digital phenotyping technology could represent a new platform for phenotype detection spotlighting new methods of data analysis. Developing novel technologies that can quantitate sensory phenotypes could present a remarkable breakthrough in understanding the genetics of sensory function. Furthermore, such tools could outline the involvement of sensory function in neuropsychiatric disorders and bolster our understanding of the genomic architecture of disease. Moreover, digital sensory phenotypes can ensure objective and continuous assessment in patients’ daily lives, facilitating improved clinical interventions. Further research into the utility of digital sensory phenotypic data, the evaluation of the accuracy of using digital technology to measure sensory phenotypes, and the efficiency of measurements in large samples is needed.

Cricually, the ethical issues that face the realization of this technology may be more difficult to overcome than the technical hurdles. Although digital technology holds substantial potential for increasing access to mental healthcare, adequate solutions for safe data transmission and storage are needed to protect participant privacy. Establishing adequate protocols for data collection, data storage, and data process, as well as a framework for securing data usage is critical from the outset. Both the academic and government sectors must endeavor to ensure that data collection and analysis efforts are pursued equitably and transparently in the common interest of humankind. Governments should pass legislation restricting the use of data and protecting participants’ privacy. While some researchers maintain a hopeful view of this new technology [157], its fruition relies upon advances in data security adequate to protect participants' privacy and to serve our common interests.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

ACKNOWLEDGE

We thank Richard F. Kopp and Liz Kuney from SUNY Upstate Medical University, for their remarkably helpful comments and language editing contributions, which greatly improved the manuscript.

FUNDING

This work was supported by the National Natural Science Foundation of China (Grant Nos. 31970572, 31571312 and 81401114), the National Key

R&D Project of China (Grant No. 2016YFC1306000), Innovation-driven Project of Central South University (Grant Nos. 2015CXS034 and 2018CX033), Hunan Provincial Natural Science Foundation of China (Grant No. 2019JJ40404) (to C. Chen), and the National Natural Science Foundation of China (Grant No. 31871276), the National Key R&D Project of China (Grant No. 2017YFC0908701) (to C. Liu), and the Fundamental Research Funds for the Central Universities of Central South University (Grant No. 1053320184146).

REFERENCES

1. Flint J, Munafo MR. The endophenotype concept in psychiatric genetics. Psychol Med. 2007;37(2):163-80.
2. Kanes S, Tokarczyk J, Chinitz J, Turetsky B, Moberg P, Bucan M, et al. Olfaction: towards a novel mouse endophenotypic model of schizophrenia. Schizophr Res. 2003;1(60):109.
3. Bedwell JS, Brown JM, Miller LS. The magnocellular visual system and schizophrenia: what can the color red tell us? Schizophr Res. 2003;63(3):273-84.
4. Kathmann N, Hochrein A, Uwer R, Bondy B. Deficits in gain of smooth pursuit eye movements in schizophrenia and affective disorder patients and their unaffected relatives. Am J Psychiatry. 2003;160(4):696-702.
5. Wells HRR, Freidin MB, Zainul Abidin FN, Payton A, Dawes P, Munro KJ, et al. GWAS Identifies 44 Independent Associated Genomic Loci for Self-Reported Adult Hearing Difficulty in UK Biobank. Am J Hum Genet. 2019;105(4):788-802.
6. Torous J, Keshavan M. A new window into psychosis: The rise digital phenotyping, smartphone assessment, and mobile monitoring. Schizophr Res. 2018;197:67-8.
7. Torous J, Firth J, Mueller N, Onnela JP, Baker JT. Methodology and Reporting of Mobile Heath and Smartphone Application Studies for Schizophrenia. Harv Rev Psychiatry. 2017;25(3):146-54.
8. Onnela JP, Rauch SL. Harnessing Smartphone-Based Digital Phenotyping to Enhance Behavioral and Mental Health. Neuropsychopharmacology. 2016;41(7):1691-6.
9. Ferreri F, Bourla A, Mouchabac S, Karila L. e-Addictology: An Overview of New Technologies for Assessing and Intervening in Addictive Behaviors. Front Psychiatry. 2018;9:51.
10. Jain SH, Powers BW, Hawkins JB, Brownstein JS. The digital phenotype. Nat Biotechnol. 2015;33(5):462-3.
11. Huckvale K, Venkatesh S, Christensen HJNDM. Toward clinical digital phenotyping: a timely opportunity to consider purpose, quality, and safety. NPJ Digit Med. 2019;2(1):1-11.
12. Melnik A, Hairston WD, Ferris DP, Konig P. EEG correlates of sensorimotor processing: independent components involved in sensory and motor processing. Sci Rep. 2017;7(1):4461.
13. Reitan RM, Wolfson D. The significance of sensory-motor functions as

indicators of brain dysfunction in children. Arch Clin Neuropsychol. 2003;18(1):11-8.
14. Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. BMC Med. 2013;11:126.
15. Wing L, Gould J, Gillberg C. Autism spectrum disorders in the DSM-V: better or worse than the DSM-IV? Res Dev Disabil. 2011;32(2):768-73.
16. Fisch GS. Whither the genotype-phenotype relationship? An historical and methodological appraisal. Am J Med Genet C. 2017;175(3):343-53.
17. Geschwind DH. Genetics of autism spectrum disorders. Trends Cogn Sci. 2011;15(9):409-16.
18. Howlin P. Autism Spectrum Disorders D.G. Amaral, G. Dawson & D.H. Geschwind New York: Oxford University Press, 2011. pp. 1446, £150.00 (hb). ISBN: 978-19-537182-6. Child Adolesc Ment Health. 2012;17(4):256.
19. Visscher PM, Wray NR, Zhang Q, Sklar P, McCarthy MI, Brown MA, et al. 10 Years of GWAS Discovery: Biology, Function, and Translation. Am J Hum Genet. 2017;101(1):5-22.
20. Gottesman, II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry. 2003;160(4):636-45.
21. Glahn DC, Knowles EE, McKay DR, Sprooten E, Raventos H, Blangero J, et al. Arguments for the sake of endophenotypes: examining common misconceptions about the use of endophenotypes in psychiatric genetics. Am J Med Genet B. 2014;165b(2):122-30.
22. Braff DL, Geyer MA, Swerdlow NR. Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies. Psychopharmacology. 2001;156(2-3):234-58.
23. Braff DL, Freedman R. Endophenotypes in studies of the genetics of schizophrenia. In Neuropsychopharmacology: The Fifth Generation of Progress. Philadelphia (US): Williams and Wilkins; 2002. p. 703-16.
24. Greenwood TA, Shutes-David A, Tsuang DW. Endophenotypes in Schizophrenia: Digging Deeper to Identify Genetic Mechanisms. J Psychiatr Brain Sci. 2019;4(2):e190005. doi: 10.20900/jpbs.20190005
25. Braff DL, Tamminga CA. Endophenotypes, Epigenetics, Polygenicity and More: Irv Gottesman's Dynamic Legacy. Schizophr Bull. 2017;43(1):10-6.
26. Myles-Worsley M. P50 sensory gating in multiplex schizophrenia families from a Pacific island isolate. Am J Psychiatry. 2002;159(12):2007-12.
27. Braff DL, Freedman R, Schork NJ, Gottesman II. Deconstructing schizophrenia: an overview of the use of endophenotypes in order to understand a complex disorder. Schizophr Bull. 2007;33(1):21-32.
28. Siegel C, Waldo M, Mizner G, Adler LE, Freedman R. Deficits in sensory gating in schizophrenic patients and their relatives. Evidence obtained with auditory evoked responses. Arch Gen Psychiatry. 1984;41(6):607-12.
29. Clementz BA, Geyer MA, Braff DL. Poor P50 suppression among schizophrenia patients and their first-degree biological relatives. Am J Psychiatry. 1998;155(12):1691-4.

30. Clementz BA, Geyer MA, Braff DL. P50 suppression among schizophrenia and normal comparison subjects: a methodological analysis. Biol Psychiatry. 1997;41(10):1035-44.
31. Clementz BA, Geyer MA, Braff DL. Multiple site evaluation of P50 suppression among schizophrenia and normal comparison subjects. Schizophr Res. 1998;30(1):71-80.
32. Judd LL, McAdams L, Budnick B, Braff DL. Sensory gating deficits in schizophrenia: new results. Am J Psychiatry. 1992;149(4):488-93.
33. Waldo MC, Adler LE, Freedman R. Defects in auditory sensory gating and their apparent compensation in relatives of schizophrenics. Schizophr Res. 1988;1(1):19-24.
34. Leonard S, Freedman R. Genetics of chromosome 15q13-q14 in schizophrenia. Biol Psychiatry. 2006;60(2):115-22.
35. Olincy A, Harris JG, Johnson LL, Pender V, Kongs S, Allensworth D, et al. Proof-of-concept trial of an alpha7 nicotinic agonist in schizophrenia. Arch Gen Psychiatry. 2006;63(6):630-8.
36. Gershon ES, Pearlson G, Keshavan MS, Tamminga C, Clementz B, Buckley PF, et al. Genetic analysis of deep phenotyping projects in common disorders. Schizophr Res. 2018;195:51-7.
37. Chen C, Gershon ES, ediors. Special Issue "Deep Phenotyping of Psychiatric Diseases" [special issue]. J Psychiatry Brain Sci. 2018. Available from: https://jpbs.hapres.com/SpecialIssuesDPPD.aspx. Accessed 2020 Jun 28.
38. Tamminga CA, Ivleva EI, Keshavan MS, Pearlson GD, Clementz BA, Witte B, et al. Clinical phenotypes of psychosis in the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP). Am J Psychiatry. 2013;170(11):1263-74.
39. Bearden CE, Thompson PM. Emerging Global Initiatives in Neurogenetics: The Enhancing Neuroimaging Genetics through Meta-analysis (ENIGMA) Consortium. Neuron. 2017;94(2):232-6.
40. Brewer WJ, Pantelis C, Anderson V, Velakoulis D, Singh B, Copolov DL, et al. Stability of olfactory identification deficits in neuroleptic-naive patients with first-episode psychosis. Am J Psychiatry. 2001;158(1):107-15.
41. Moberg PJ, Kamath V, Marchetto DM, Calkins ME, Doty RL, Hahn CG, et al. Meta-analysis of olfactory function in schizophrenia, first-degree family members, and youths at-risk for psychosis. Schizophr Bull. 2014;40(1):50-9.
42. Baranek GT, David FJ, Poe MD, Stone WL, Watson LR. Sensory Experiences Questionnaire: discriminating sensory features in young children with autism, developmental delays, and typical development. J Child Psychol Psychiatry. 2006;47(6):591-601.
43. Ben-Sasson A, Cermak SA, Orsmond GI, Tager-Flusberg H, Carter AS, Kadlec MB, et al. Extreme sensory modulation behaviors in toddlers with autism spectrum disorders. Am J Occup Ther. 2007;61(5):584-92.
44. Liss M, Saulnier C, Fein D, Kinsbourne M. Sensory and attention abnormalities in autistic spectrum disorders. Autism. 2006;10(2):155-72.
45. Green SA, Hernandez L, Bookheimer SY, Dapretto M. Reduced modulation of

thalamocortical connectivity during exposure to sensory stimuli in ASD. Autism Res. 2017;10(5):801-9.

46. Lencer R, Sprenger A, Reilly JL, McDowell JE, Rubin LH, Badner JA, et al. Pursuit eye movements as an intermediate phenotype across psychotic disorders: Evidence from the B-SNIP study. Schizophr Res. 2015;169(1-3):326-33.
47. Velly AM, Mohit S. Epidemiology of pain and relation to psychiatric disorders. Prog Neuropsychopharmacol Biol psychiatry. 2018;87(Pt B):159-67.
48. Sheng J, Liu S, Wang Y, Cui R, Zhang X. The Link between Depression and Chronic Pain: Neural Mechanisms in the Brain. Neural Plast. 2017;2017:9724371.
49. Meerwijk EL, Ford JM, Weiss SJ. Brain regions associated with psychological pain: implications for a neural network and its relationship to physical pain. Brain Imaging Behav. 2013;7(1):1-14.
50. Carter O, Bennett D, Nash T, Arnold S, Brown L, Cai RY, et al. Sensory integration deficits support a dimensional view of psychosis and are not limited to schizophrenia. Transl Psychiatry. 2017;7(5):e1118.
51. Quednow BB, Brinkmeyer J, Mobascher A, Nothnagel M, Musso F, Grunder G, et al. Schizophrenia risk polymorphisms in the TCF4 gene interact with smoking in the modulation of auditory sensory gating. Proc Natl Acad Sci U S A. 2012;109(16):6271-6.
52. Ethridge LE, Hamm JP, Pearlson GD, Tamminga CA, Sweeney JA, Keshavan MS, et al. Event-related potential and time-frequency endophenotypes for schizophrenia and psychotic bipolar disorder. Biol Psychiatry. 2015;77(2):127-36.
53. Enoch MA, White KV, Waheed J, Goldman D. Neurophysiological and genetic distinctions between pure and comorbid anxiety disorders. Depress Anxiety. 2008;25(5):383-92.
54. Moberg PJ, Li M, Kanes SJ, Gur RE, Kamath V, Turetsky BI. Association of schizophrenia with the phenylthiocarbamide taste receptor haplotype on chromosome 7q. Psychiatr Genet. 2012;22(6):286-9.
55. Compton MT, Ionescu DF, Broussard B, Cristofaro SL, Johnson S, Haggard PJ, et al. An examination of associations between the inability to taste phenylthiocarbamide (PTC) and clinical characteristics and trait markers in first-episode, nonaffective psychotic disorders. Psychiatry Res. 2013;209(1):27-31.
56. Brewer WJ, Wood SJ, McGorry PD, Francey SM, Phillips LJ, Yung AR, et al. Impairment of olfactory identification ability in individuals at ultra-high risk for psychosis who later develop schizophrenia. Am J Psychiatry. 2003;160(10):1790-4.
57. Doty RL, Reyes PF, Gregor T. Presence of both odor identification and detection deficits in Alzheimer's disease. Brain Res Bull. 1987;18(5):597-600.
58. Guclu B, Tanidir C, Canayaz E, Guner B, Ipek Toz H, Uneri OS, et al. Tactile processing in children and adolescents with obsessive-compulsive disorder. Somatosens Mot Res. 2015;32(3):163-71.

59. Thornton-Wells TA, Cannistraci CJ, Anderson AW, Kim CY, Eapen M, Gore JC, et al. Auditory attraction: activation of visual cortex by music and sound in Williams syndrome. Am J Intellect Dev Disabil. 2010;115(2):172-89.
60. Bertelsen B, Oranje B, Melchior L, Fagerlund B, Werge TM, Mikkelsen JD, et al. Association Study of CHRNA7 Promoter Variants with Sensory and Sensorimotor Gating in Schizophrenia Patients and Healthy Controls: A Danish Case-Control Study. Neuromol Med. 2015;17(4):423-30.
61. Cabranes JA, Ancin I, Santos JL, Sanchez-Morla E, Garcia-Jimenez MA, Lopez-Ibor JJ, et al. No effect of polymorphisms in the non-duplicated region of the CHRNA7 gene on sensory gating P50 ratios in patients with schizophrenia and bipolar disorder. Psychiatry Res. 2013;205(3):276-8.
62. Garcia-Blanco A, Salmeron L, Perea M. Inhibitory Control for Emotional and Neutral Scenes in Competition: An Eye-Tracking Study in Bipolar Disorder. Biol Psychol. 2017;127:82-8.
63. Hall MH, Schulze K, Sham P, Kalidindi S, McDonald C, Bramon E, et al. Further evidence for shared genetic effects between psychotic bipolar disorder and P50 suppression: a combined twin and family study. Am J Med Genet B. 2008;147b(5):619-27.
64. Hamm JP, Ethridge LE, Boutros NN, Keshavan MS, Sweeney JA, Pearlson GD, et al. Diagnostic specificity and familiality of early versus late evoked potentials to auditory paired stimuli across the schizophrenia-bipolar psychosis spectrum. Psychophysiology. 2014;51(4):348-57.
65. Bylsma FW, Moberg PJ, Doty RL, Brandt J. Odor identification in Huntington's disease patients and asymptomatic gene carriers. J Neuropsychiatry Clin Neurosci. 1997;9(4):598-600.
66. Bachmann S, Weisbrod M, Rohrig M, Schroder J, Thomas C, Scherg M, et al. MEG does not reveal impaired sensory gating in first-episode schizophrenia. Schizophr Res. 2010;121(1-3):131-8.
67. Bortolon C, Capdevielle D, Salesse RN, Raffard S. Self-Face Recognition in Schizophrenia: An Eye-Tracking Study. Front Hum Neurosci. 2016;10:3.
68. Brewer WJ, Lin A, Moberg PJ, Smutzer G, Nelson B, Yung AR, et al. Phenylthiocarbamide (PTC) perception in ultra-high risk for psychosis participants who develop schizophrenia: testing the evidence for an endophenotypic marker. Psychiatry Res. 2012;199(1):8-11.
69. Brockhaus-Dumke A, Schultze-Lutter F, Mueller R, Tendolkar I, Bechdolf A, Pukrop R, et al. Sensory gating in schizophrenia: P50 and N100 gating in antipsychotic-free subjects at risk, first-episode, and chronic patients. Biol Psychiatry. 2008;64(5):376-84.
70. Crespo-Facorro B, Paradiso S, Andreasen NC, O'Leary DS, Watkins GL, Ponto LL, et al. Neural mechanisms of anhedonia in schizophrenia: a PET study of response to unpleasant and pleasant odors. JAMA. 2001;286(4):427-35.
71. Erwin RJ, Turetsky BI, Moberg P, Gur RC, Gur RE. P50 abnormalities in schizophrenia: relationship to clinical and neuropsychological indices of attention. Schizophr Res. 1998;33(3):157-67.

72. Hazlett EA, Rothstein EG, Ferreira R, Silverman JM, Siever LJ, Olincy A. Sensory gating disturbances in the spectrum: similarities and differences in schizotypal personality disorder and schizophrenia. Schizophr Res. 2015;161(2-3):283-90.
73. Hermens DF, Ward PB, Hodge MA, Kaur M, Naismith SL, Hickie IB. Impaired MMN/P3a complex in first-episode psychosis: cognitive and psychosocial associations. Prog Neuropsychopharmacol Biol Psychiatry. 2010;34(6):822-9.
74. Keri S, Beniczky S, Kelemen O. Suppression of the P50 evoked response and neuregulin 1-induced AKT phosphorylation in first-episode schizophrenia. Am J Psychiatry. 2010;167(4):444-50.
75. Kopala LC, Good KP, Torrey EF, Honer WG. Olfactory function in monozygotic twins discordant for schizophrenia. Am J Psychiatry. 1998;155(1):134-6.
76. Kopala LC, Good KP, Morrison K, Bassett AS, Alda M, Honer WG. Impaired olfactory identification in relatives of patients with familial schizophrenia. Am J Psychiatry. 2001;158(8):1286-90.
77. Lang CJ, Schwandner K, Hecht M. Do patients with motor neuron disease suffer from disorders of taste or smell? Amyotroph Lateral Scler. 2011;12(5):368-71.
78. Light GA, Swerdlow NR, Thomas ML, Calkins ME, Green MF, Greenwood TA, et al. Validation of mismatch negativity and P3a for use in multi-site studies of schizophrenia: characterization of demographic, clinical, cognitive, and functional correlates in COGS-2. Schizophr Res. 2015;163(1-3):63-72.
79. Malaspina D, Coleman E, Goetz RR, Harkavy-Friedman J, Corcoran C, Amador X, et al. Odor identification, eye tracking and deficit syndrome schizophrenia. Biol Psychiatry. 2002;51(10):809-15.
80. Martin LF, Leonard S, Hall MH, Tregellas JR, Freedman R, Olincy A. Sensory gating and alpha-7 nicotinic receptor gene allelic variants in schizoaffective disorder, bipolar type. Am J Med Genet B. 2007;144b(5):611-4.
81. Moberg PJ, Arnold SE, Doty RL, Kohler C, Kanes S, Seigel S, et al. Impairment of odor hedonics in men with schizophrenia. Am J Psychiatry. 2003;160(10):1784-9.
82. Moberg PJ, Roalf DR, Balderston CC, Kanes SJ, Gur RE, Turetsky BI. Phenylthiocarbamide perception in patients with schizophrenia and first-degree family members. Am J Psychiatry. 2005;162(4):788-90.
83. Moberg PJ, Arnold SE, Doty RL, Gur RE, Balderston CC, Roalf DR, et al. Olfactory functioning in schizophrenia: relationship to clinical, neuropsychological, and volumetric MRI measures. J Clin Exp Neuropsychol. 2006;28(8):1444-61.
84. Moberg PJ, Arnold SE, Roalf DR, Balderston CC, Abbazia J, Kohler CG, et al. Apolipoprotein E genotype and odor identification in schizophrenia. J Neuropsychiatry Clin Neurosci. 2006;18(2):231-3.
85. Moberg PJ, McGue C, Kanes SJ, Roalf DR, Balderston CC, Gur RE, et al. Phenylthiocarbamide (PTC) perception in patients with schizophrenia and first-degree family members: relationship to clinical symptomatology and

psychophysical olfactory performance. Schizophr Res. 2007;90(1-3):221-8.
86. Myles-Worsley M, Ord L, Blailes F, Ngiralmau H, Freedman R. P50 sensory gating in adolescents from a pacific island isolate with elevated risk for schizophrenia. Biol Psychiatry. 2004;55(7):663-7.
87. Phillips ML, David AS. Visual scan paths are abnormal in deluded schizophrenics. Neuropsychologia. 1997;35(1):99-105.
88. Plailly J, d'Amato T, Saoud M, Royet JP. Left temporo-limbic and orbital dysfunction in schizophrenia during odor familiarity and hedonicity judgments. NeuroImage. 2006;29(1):302-13.
89. Roalf DR, Turetsky BI, Owzar K, Balderston CC, Johnson SC, Brensinger CM, et al. Unirhinal olfactory function in schizophrenia patients and first-degree relatives. J Neuropsychiatry Clin Neurosci. 2006;18(3):389-96.
90. Roux P, Brunet-Gouet E, Passerieux C, Ramus F. Eye-tracking reveals a slowdown of social context processing during intention attribution in patients with schizophrenia. J Psychiatry Neurosci. 2016;41(2):E13-21.
91. Rupp CI, Fleischhacker WW, Kemmler G, Kremser C, Bilder RM, Mechtcheriakov S, et al. Olfactory functions and volumetric measures of orbitofrontal and limbic regions in schizophrenia. Schizophr Res. 2005;74(2-3):149-61.
92. Schneider F, Habel U, Reske M, Toni I, Falkai P, Shah NJ. Neural substrates of olfactory processing in schizophrenia patients and their healthy relatives. Psychiatry Res. 2007;155(2):103-12.
93. Thoma RJ, Hanlon FM, Moses SN, Ricker D, Huang M, Edgar C, et al. M50 sensory gating predicts negative symptoms in schizophrenia. Schizophr Res. 2005;73(2-3):311-8.
94. Thomas ML, Green MF, Hellemann G, Sugar CA, Tarasenko M, Calkins ME, et al. Modeling Deficits From Early Auditory Information Processing to Psychosocial Functioning in Schizophrenia. JAMA Psychiatry. 2017;74(1):37-46.
95. Turetsky BI, Moberg PJ, Yousem DM, Doty RL, Arnold SE, Gur RE. Reduced olfactory bulb volume in patients with schizophrenia. Am J Psychiatry. 2000;157(5):828-30.
96. Turetsky BI, Moberg PJ, Owzar K, Johnson SC, Doty RL, Gur RE. Physiologic impairment of olfactory stimulus processing in schizophrenia. Biol Psychiatry. 2003;53(5):403-11.
97. Turetsky BI, Moberg PJ, Roalf DR, Arnold SE, Gur RE. Decrements in volume of anterior ventromedial temporal lobe and olfactory dysfunction in schizophrenia. Arch Gen Psychiatry. 2003;60(12):1193-200.
98. Turetsky BI, Moberg PJ, Arnold SE, Doty RL, Gur RE. Low olfactory bulb volume in first-degree relatives of patients with schizophrenia. Am J Psychiatry. 2003;160(4):703-8.
99. Turetsky BI, Hahn CG, Arnold SE, Moberg PJ. Olfactory receptor neuron dysfunction in schizophrenia. Neuropsychopharmacology. 2009;34(3):767-74.
100. Ugur T, Weisbrod M, Franzek E, Pfuller U, Sauer H. Olfactory impairment in monozygotic twins discordant for schizophrenia. Eur Arch Psychiatry Clin

Neurosci. 2005;255(2):94-8.
101. Kohler CG, Moberg PJ, Gur RE, O'Connor MJ, Sperling MR, Doty RL. Olfactory dysfunction in schizophrenia and temporal lobe epilepsy. Neuropsychiatry Neuropsychol Behav Neurol. 2001;14(2):83-8.
102. Boutros N, Zouridakis G, Rustin T, Peabody C, Warner D. The P50 component of the auditory evoked potential and subtypes of schizophrenia. Psychiatry Res. 1993;47(3):243-54.
103. Dong J, Wyss A, Yang J, Price TR, Nicolas A, Nalls M, et al. Genome-Wide Association Analysis of the Sense of Smell in U.S. Older Adults: Identification of Novel Risk Loci in African-Americans and European-Americans. Mol Neurobiol. 2017;54(10):8021-32.
104. Dong J, Yang J, Tranah G, Franceschini N, Parimi N, Alkorta-Aranburu G, et al. Genome-wide Meta-analysis on the Sense of Smell Among US Older Adults. Medicine. 2015;94(47):e1892.
105. Kikuchi M, Miura K, Morita K, Yamamori H, Fujimoto M, Ikeda M, et al. Genome-wide Association Analysis of Eye Movement Dysfunction in Schizophrenia. Sci Rep. 2018;8(1):12347.
106. Ma Y, Li J, Yu H, Wang L, Lu T, Pan C, et al. Association of chromosome 5q21.3 polymorphisms with the exploratory eye movement dysfunction in schizophrenia. Sci Rep. 2015;5:10299.
107. Qiu L, Tian L, Pan C, Zhu R, Liu Q, Yan J, et al. Neuroanatomical circuitry associated with exploratory eye movement in schizophrenia: a voxel-based morphometric study. PLoS One. 2011;6(10):e25805.
108. Arnau-Soler A, Macdonald-Dunlop E, Adams MJ, Clarke TK, MacIntyre DJ, Milburn K, et al. Genome-wide by environment interaction studies of depressive symptoms and psychosocial stress in UK Biobank and Generation Scotland. Transl Psychiatry. 2019;9(1):14.
109. Schizophrenia Working Group of the Psychiatric Genomics C. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014;511(7510):421-7.
110. Doty RL, Frye RE, Agrawal U. Internal consistency reliability of the fractionated and whole University of Pennsylvania Smell Identification Test. Percep Psychophys. 1989;45(5):381-4.
111. Lawton M, Hu MT, Baig F, Ruffmann C, Barron E, Swallow DM, et al. Equating scores of the University of Pennsylvania Smell Identification Test and Sniffin' Sticks test in patients with Parkinson's disease. Parkinsonism Relat Disord. 2016;33:96-101.
112. Luck SJ. An introduction to the event-related potential technique. Cambridge (US): MIT press; 2014.
113. Sur S, Sinha VK. Event-related potential: An overview. Ind Psychiatry J. 2009;18(1):70-3.
114. Mutanen TP, Metsomaa J, Liljander S, Ilmoniemi RJ. Automatic and robust noise suppression in EEG and MEG: The SOUND algorithm. NeuroImage. 2018;166:135-51.

115. Insel TR. Digital Phenotyping: Technology for a New Science of Behavior. JAMA. 2017;318(13):1215-6.
116. Torous J, Friedman R, Keshavan M. Smartphone ownership and interest in mobile applications to monitor symptoms of mental health conditions. JMIR mHealth uHealth. 2014;2(1):e2.
117. Bidargaddi N, Musiat P, Makinen VP, Ermes M, Schrader G, Licinio J. Digital footprints: facilitating large-scale environmental psychiatric research in naturalistic settings through data from everyday technologies. Mol Psychiatry. 2017;22(2):164-9.
118. Csikszentmihalyi M, Larson R. Validity and reliability of the Experience-Sampling Method. J Nerv Ment Dis. 1987;175(9):526-36.
119. Litt MD, Cooney NL, Morse P. Ecological momentary assessment (EMA) with treated alcoholics: methodological problems and potential solutions. Health Psychol. 1998;17(1):48-52.
120. Staples P, Torous J, Barnett I, Carlson K, Sandoval L, Keshavan M, et al. A comparison of passive and active estimates of sleep in a cohort with schizophrenia. NPJ Schizophr. 2017;3(1):37.
121. Dickerson RF, Gorlin EI, Stankovic JA, editors. Empath: a continuous remote emotional health monitoring system for depressive illness. In: Proceedings of the 2nd Conference on Wireless Health; 2011 October 10-13; San Diego, USA.
122. McIntyre G, Göcke R, Hyett M, Green M, Breakspear M, editors. An approach for automatically measuring facial activity in depressed subjects. Presented at 2009 3rd International Conference on Affective Computing and Intelligent Interaction and Workshops; 2009 Sep 10-12; Amsterdam, The Netherlands.
123. Saeb S, Lattie EG, Schueller SM, Kording KP, Mohr DC. The relationship between mobile phone location sensor data and depressive symptom severity. PeerJ. 2016;4:e2537.
124. Jacobson NC, Weingarden H, Wilhelm S. Using Digital Phenotyping to Accurately Detect Depression Severity. J Nerv Ment Dis. 2019;207(10):893-6.
125. Beiwinkel T, Kindermann S, Maier A, Kerl C, Moock J, Barbian G, et al. Using Smartphones to Monitor Bipolar Disorder Symptoms: A Pilot Study. JMIR Ment Health. 2016;3(1):e2.
126. Gruenerbl A, Osmani V, Bahle G, Carrasco JC, Oehler S, Mayora O, et al., editors. Using smart phone mobility traces for the diagnosis of depressive and manic episodes in bipolar patients. In: Proceedings of the 5th Augmented Human International Conference; 2014 Mar 7-9; Kobe, Japan.
127. Barnett I, Torous J, Staples P, Sandoval L, Keshavan M, Onnela JP. Relapse prediction in schizophrenia through digital phenotyping: a pilot study. Neuropsychopharmacology. 2018;43(8):1660-6.
128. Minassian A, Henry BL, Geyer MA, Paulus MP, Young JW, Perry W. The quantitative assessment of motor activity in mania and schizophrenia. J Affect Disord. 2010;120(1-3):200-6.
129. Hswen Y, Naslund JA, Brownstein JS, Hawkins JB. Online Communication about Depression and Anxiety among Twitter Users with Schizophrenia:

Preliminary Findings to Inform a Digital Phenotype Using Social Media. Psychiatr Q. 2018;89(3):569-80.

130. van der Wee NJA, Bilderbeck AC, Cabello M, Ayuso-Mateos JL, Saris IMJ, Giltay EJ, et al. Working definitions, subjective and objective assessments and experimental paradigms in a study exploring social withdrawal in schizophrenia and Alzheimer's disease. Neurosci Biobehav Rev. 2019;97:38-46.
131. Bedi G, Carrillo F, Cecchi GA, Slezak DF, Sigman M, Mota NB, et al. Automated analysis of free speech predicts psychosis onset in high-risk youths. NPJ Schizophr. 2015;1:15030.
132. Gunn JF III, Lester D. Using google searches on the internet to monitor suicidal behavior. J Affect Disord. 2013;148(2-3):411-2.
133. Adhikari S, Stark DE. Video-based eye tracking for neuropsychiatric assessment. Ann N Y Acad Sci. 2017;1387(1):145-52.
134. Koppe G, Guloksuz S, Reininghaus U, Durstewitz D. Recurrent Neural Networks in Mobile Sampling and Intervention. Schizophr Bull. 2019;45(2):272-6.
135. Torous J, Kiang MV, Lorme J, Onnela JP. New Tools for New Research in Psychiatry: A Scalable and Customizable Platform to Empower Data Driven Smartphone Research. JMIR Ment Health. 2016;3(2):e16.
136. Rono HK, Bastawrous A, Macleod D, Wanjala E, Di Tanna GL, Weiss HA, et al. Smartphone-based screening for visual impairment in Kenyan school children: a cluster randomised controlled trial. Lancet Glob Health. 2018;6(8):e924-32.
137. Zhao L, Stinnett SS, Prakalapakorn SG. Visual Acuity Assessment and Vision Screening Using a Novel Smartphone Application. J Pediatr. 2019;213:203-10.e1.
138. Toh WL, Thomas N, Rossell SL. Auditory verbal hallucinations in bipolar disorder (BD) and major depressive disorder (MDD): A systematic review. J Affect Disord. 2015;184:18-28.
139. Krafka K, Khosla A, Kellnhofer P, Kannan H, Bhandarkar S, Matusik W, et al., editors. Eye tracking for everyone. In: Proceedings of the IEEE conference on computer vision and pattern recognition; 2016 Jun 27-30; Las Vegas, USA.
140. Strobl MA, Lipsmeier F, Demenescu LR, Gossens C, Lindemann M, De Vos M. Look me in the eye: evaluating the accuracy of smartphone-based eye tracking for potential application in autism spectrum disorder research. Biomed Eng Online. 2019;18(1):51.
141. Lai H-Y, Saavedra-Pena G, Sodini CG, Sze V, Heldt T. Measuring Saccade Latency using Smartphone Cameras. IEEE J Biomed Health Inform. 2019;24:3:885-97.
142. Teki S, Kumar S, Griffiths TD. Large-Scale Analysis of Auditory Segregation Behavior Crowdsourced via a Smartphone App. PLoS One. 2016;11(4):e0153916.
143. De Sousa KC, Swanepoel DW, Moore DR, Smits C. A smartphone national hearing test: Performance and characteristics of users. Am J Audiol.

2018;27(3S):448-54.
144. Barczik J, Serpanos YC. Accuracy of smartphone self-hearing test applications across frequencies and earphone styles in adults. Am J Audiol. 2018;27(4):570-80.
145. Button KS, Ioannidis JP, Mokrysz C, Nosek BA, Flint J, Robinson ES, et al. Power failure: why small sample size undermines the reliability of neuroscience. Nat Rev Neurosci. 2013;14(5):365-76.
146. Denny JC, Bastarache L, Roden DM. Phenome-Wide Association Studies as a Tool to Advance Precision Medicine. Ann Rev Genom Hum Genet. 2016;17:353-73.
147. Smoller JW. The use of electronic health records for psychiatric phenotyping and genomics. Am J Med Genet B. 2018;177(7):601-12.
148. Grindrod K, Boersema J, Waked K, Smith V, Yang J, Gebotys C. Locking it down: The privacy and security of mobile medication apps. Can Pharm J. 2017;150(1):60-6.
149. Huckvale K, Torous J, Larsen ME. Assessment of the Data Sharing and Privacy Practices of Smartphone Apps for Depression and Smoking Cessation. JAMA Netw Open. 2019;2(4):e192542.
150. Barnett S, Huckvale K, Christensen H, Venkatesh S, Mouzakis K, Vasa R. Intelligent Sensing to Inform and Learn (InSTIL): A Scalable and Governance-Aware Platform for Universal, Smartphone-Based Digital Phenotyping for Research and Clinical Applications. J Med Int Res. 2019;21(11):e16399.
151. Gillon R. Medical ethics: four principles plus attention to scope. BMJ. 1994;309(6948):184-8.
152. Huckvale K, Prieto JT, Tilney M, Benghozi PJ, Car J. Unaddressed privacy risks in accredited health and wellness apps: a cross-sectional systematic assessment. BMC Med. 2015;13:214.
153. Wang Y, Kosinski M. Deep neural networks are more accurate than humans at detecting sexual orientation from facial images. J Pers Soc Psychol. 2018;114(2):246-57.
154. Martinez-Martin N, Insel TR, Dagum P, Greely HT, Cho MK. Data mining for health: staking out the ethical territory of digital phenotyping. NPJ Digit Med. 2018;1:68.
155. Shah H. Use our personal data for the common good. Nature. 2018;556(7699):7.
156. Dyson FJ. Imagined worlds. Cambridge (US): Harvard University Press; 1998.
157. Ebner-Priemer U, Santangelo P. Digital phenotyping: hype or hope? Lancet Psychiatry. 2020;7(4):297-9. doi: 10.1016/S2215-0366(19)30380-3

How to cite this article:
Dai J, Chen Y, Xia C, Zhou J, Liu C, Chen C. Digital Sensory Phenotyping for Psychiatric Disorders. J Psychiatry Brain Sci. 2020;5:e200015. https://doi.org/10.20900/jpbs.20200015