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Review article

Ambulatory assessment as a means of longitudinal phenotypes characterization in psychiatric disorders

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ABSTRACT

Ambulatory Assessment (AA) comprises the use of in-field methods to assess individuals' behavior, physiology, and the experience as they unfold in naturalistic settings. We propose that AA is favorable for the investigation of gene–environment interactions and for the search for endophenotypes, being able to assess the *experienced* environment and to track basic regulatory processes, such as stress reactivity, affective instability, and reward experience, which are potential common factors that underlie psychiatric disorders.

In this article, we (a) first describe briefly the rationale of AA and summarize the key advantages of the approach, (b) highlight within-subject regulatory processes, such as stress reactivity, affective instability, and reward experience, (c) describe studies that used AA to examine genetic influences in psychiatric disorders, and (d) briefly review longitudinal studies that have investigated phenotypes of psychiatric disorders.

The reported studies yielded promising, although sometimes inconclusive evidence for genetic effects on endophenotypes of psychiatric disorders. Moreover, most studies were twin or family studies, especially in stress-sensitivity research; thus, it is unclear which specific single nucleotide polymorphisms contribute to the endophenotypes of psychiatric disorders. We do hope that within-subject regulatory processes will enable us to clarify the fundamental psychological dimensions that cut across traditional disorders and link them to their genetic underpinnings.

Contents

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1. Introduction

The unsuccessful search for direct associations between genotypes and psychiatric disorders as phenotypes has resulted in both, the investigation of gene–environment interactions and the search for endophenotypes (Caspi and Moffitt, 2006) with potential stronger genetic underpinnings. In this article, we introduce a methodology that offers key advantages for both endeavors: Ambulatory Assessment. *Ambulatory Assessment* (AA) comprises the use of in-field methods to assess the ongoing behavior, physiology, experience and environmental aspects of individuals in naturalistic or unconstrained settings (Society for Ambulatory Assessment, 2014; www.ambulatory-assessment.org). AA uses ecologically valid tools to understand biopsychosocial processes as they naturally unfold in time and context.

Regarding endophenotypes, AA is favorable because it can track basic regulatory processes, such as stress reactivity, affective instability, and reward experience, which are presumably factors that underlie psychiatric disorders. With the Research domain criteria strategic initiative (RDoC: Cuthbert and Insel, 2013; Cuthbert and Kozak, 2013) of the National Institute of Mental Health (NIMH), substantial emphasis has been placed on replacing a categorical approach to mental disorders with the classification of psychopathology based on dimensions of observable behavior and neurobiological measures. Although RDoC falls short in understanding human behaviors as dynamical processes that unfold in everyday life, it emphasizes a regulatory process perspective. AA is especially well suited to investigate basic regulatory processes, such as stress reactivity, affective instability, and reward experience, because multiple self-reports are retrieved over time from each subject which enables the analysis of within-subject regulatory processes. There are multiple lines of evidence (Trull and Ebner-Priemer, 2013; van Os et al., 2014) that these within-subject regulatory processes are better suited to explain psychopathology, are better predictors of treatment success and relapse, and are most likely more powerful to demonstrate gene–environment interactions.

In the following paper, we (a) briefly describe the rationale of AA and summarize the key advantages of this approach, (b) highlight within-subject regulatory processes, such as stress reactivity, affective instability, and reward experience, (c) review studies that used AA to examine genetic influences in psychiatric disorders, and (d) briefly describe longitudinal studies that have investigated phenotypes of psychiatric disorders.

2. Key features of Ambulatory Assessment

Whereas AA comprises a wide range of specific methods, these methods typically share a common set of key features. At its core, AA represents *real-life*, *real-time* and *cross-domain* assessments. Moreover, the choices among different sampling schemes (e.g., protocol at which time points or events experience, behavior, and physiology will be sampled) and advanced statistical procedures (e.g., mixed regression) provide researchers with ideal tools to advance the understanding of within-subject processes and their interaction with genetics.

2.1. Going real life

Whereas laboratory findings have their strengths in the rigorous control of confounders and meticulous experimental setups, a potential lack of generalizability to real life phenomena due to the more "artificial" setup is a major problem. AA aims to capture and investigate processes as they naturally unfold in daily life, thus providing critical insights and findings of high ecological validity (Brunswik, 1941), that is findings that generalize to real-life processes outside research. Hence, AA is a research approach that offers crucial complimentary evidence to experimental research in the laboratory. This added value of AA has been demonstrated in a wide range of research questions, including the white coat hypertension phenomenon: The office hypertension or white coat effect, which refers to the finding that blood pressure readings made by a physician in a clinic or laboratory setting are higher compared with values recorded in 24-hr ambulatory blood pressure assessment, has been replicated in hundreds of studies. The implication is that hundreds of thousands of individuals may have been misdiagnosed and possibly mistreated because of the white coat effect (Hansen et al., 2006). This effect serves as an instructive example of how fallible it can be to generalize solely on the basis of laboratory experiments or findings in artificial situations.

Moreover, many processes that are considered key for understanding mental health and psychiatric disorders can almost exclusively be studied in real life, such as interactions between an individual's psychological processes and his or her social environment. With genotype × environment interactions at the core of research focused on the genetics that underlies psychiatric disorders, AA is a most promising candidate to gain novel insights and advance theoretical premises in this field.

2.2. Going real time

In AA, data are typically captured in real-time in the sense of continuous monitoring of physiological signals or as momentary self-reports (e.g., prompting participants to rate their current affective state). The real-time nature of AA offers opportunities to study processes that unfold over time in vivo and with regards to avoiding several pitfalls of study designs built on "retrospective" assessments. For example, momentary self-reports reduce the effect of cognitive heuristics and individual biases that typically afflict retrospective self-reports (Schwarz, 2007) such as "traditional" questionnaires and conventional measures in Patient Reported Outcome Research. Several seminal studies have impressively demonstrated that retrospective, "delayed" self-reporting of essentially fluctuating and dynamic states (such as affect, distress, or bodily or mental health symptoms) systematically deviates from the individuals' experiences if assessed in real time (Redelmeier and Kahneman, 1996; Schwarz and Strack, 1999).

Recent advances in mobile computing technology offer additional advantages for real time features in AA by allowing real time analyses of captured data, such as integrating and processing of physiological and activity signals (e.g., computing the heart rate variability from the heart rate signal, characterizing accelerometry data in terms of the patterns of physical activity, or advanced real time artifact and signal noise control). These advanced real time analysis capabilities provide the foundation for even more sophisticated AA designs (Ebner-Priemer et al., 2013) in that the domains of assessment may be connected in a real time fashion. For example, heart rate variability may be used to trigger self-reports. To do this, heart rate variability is calculated in real time. If certain thresholds are surpassed, the physiological recorder-analyzer-system sends trigger to the smartphone to start questions, for example on affect, location and current activity. This approach, sometimes also called interactive ambulatory assessments, enables to maximize the variance of the physiological variable of interest during e-diary requests. Because of the importance of stress reactivity and the vulnerability model in current research focused on the genetics of psychiatric disorders, this real-time approach of linking