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How to assess stress biomarkers for idiographic research?

Sonja L. van Ockenburg, Sanne H. Booij, Harriëtte Riese, Judith G.M. Rosmalen*, Karin A.M. Janssens

Interdisciplinary Center Psychopathology and Emotion regulation, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

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ABSTRACT

Associations between stress-related biomarkers, like cortisol or catecholamines, and somatic or psychological symptoms have often been examined at the group level. Studies using this nomothetic approach reported equivocal findings, which may be due to high levels of intra-individual variance of stress biomarkers. More importantly, analyses at the group level provide information about the average patient, but do not necessarily have meaning for individual patients. An alternative approach is to examine data at the level of individual patients in so-called idiographic research. This method allows identifying individuals in whom symptoms are explained by preceding alterations in specific stress biomarkers, based on time series of symptoms and stress biomarkers. To create time series of sufficient length for statistical analysis, many subsequent stress biomarker measurements are needed for each participant. In the current paper, different matrices (i.e. saliva, urine, nail and hair) are discussed in light of their applicability for idiographic research. This innovative approach might lead to promising new insights in the association between stress biomarkers and psychological or somatic symptoms. New collection tools for stress biomarkers, like the use of sweat pads, automated microdialysis systems, dried blood spots, or smartphone applications, might contribute to the feasibility and implementation of idiographic research in the future.

1. Examining psychoneuroendocrinology at the level of individuals

Since the last half of the previous century, stress-related peripheral biomarkers, like cortisol and catecholamines, have been examined in patients suffering from psychological and somatic disorders (Tak et al., 2009b; Vogelzangs et al., 2010; Vrshek-Schallhorn et al., 2013). In these studies, it is generally assumed that alterations found at the group level are present in all individual patients. However, in order to generalize findings at the group level to the level of the individual, two assumptions have to be met: (1) the study population has to be homogeneous, and (2) the processes under study should have a stable mean and (co) variance function over time (Molenaar, 2004). Regarding the first assumption, studies provide evidence for significant intra-individual heterogeneity with regard to the importance of stress biomarkers in disease (Kudielka et al., 2009; Tak et al., 2009a,b). Differences between groups of patients and controls are often smaller than the differences within these groups. The second assumption, stability over time, most likely does not hold for most stress biomarkers. Studies looking at within-individual stability of cortisol levels over time show large day-to-day fluctuations, shifts in a person's mean level over the course of days, and cyclical trends (Platje et al., 2013; Schubert et al., 2012). Moreover, the psychological processes to which these stress biomarkers are often linked are inherently unstable over time (Molenaar and Campbell, 2009). When the process under study violates the homogeneity or stability assumption, findings at the population level cannot be generalized to the individual level. A new approach in the field of psychoneuroendocrinology, adopted from fields such as econometrics and engineering, might aid overcoming these problems. This time-series method, which is an idiographic approach, aims at identifying relationships within individuals. The method can for example be used to link multiple repeated measurements (time series) of a suspected stress biomarker to somatic or psychological symptoms within a single patient. Such an approach provides information about a single patient and thus allows determining whether a biomarker is related to the symptoms in that particular patient. These analyses do not need a priori decisions about which variable is the determinant and which variable the outcome,

* Corresponding author at: Interdisciplinary Center Psychopathology and Emotion regulation, CC 72, University of Groningen, University Medical Center Groningen, CC 72, PO Box 30001, 9700 RB Groningen, The Netherlands. Fax: +31 50 361 9722.
E-mail address: j.g.m.rosmalen@umcg.nl (J.G.M. Rosmalen).

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Table 1
Differences between idiographic and nomothetic research with regard to psychoneuroendocrinologic research.

	Idiographic	Nomothetic
Analysis level	Individual level	Group level
Research questions	E.g. Does a rise in cortisol level predict deterioration of mood in this participant?	E.g. Do participants with low mood have higher cortisol levels?
Power	Determined by number of observations for each individual	Determined by number of participants and number of observations for each individual
Number of data points for each participant	As high as possible, at least 30 for vector autoregressive analyses	Possible with one observation for each participant
Confounders	Factors that fluctuate within the measurement period (e.g. weather, stressful events, number of cigarettes smoked)	Factors that differ between participants (e.g age, gender, glucocorticoid sensitivity, biological challenge)
Practical consequences	Data preferably equidistant and stationary. Highly intensive collection period, thus, concessions have to be made to make collection feasible (e.g. no food intake 30 min before saliva sample)	Data do not need to be stationary or equidistant. Less intensive collection for individuals, thus, less concessions (e.g. no food intake 2 h before saliva sample)
Statistical techniques	E.g. Vector autoregressive models, unified structural equation models, dynamic models	E.g. Regression models, multilevel models, structural equation models

implying that the effect of physiological alterations on symptom fluctuations, and the effect of fluctuations in symptoms on physiology can be modeled simultaneously. Therefore, idiographic research is ideally suited for the field of psychoneuroendocrinology, in which it is often unclear whether physiological alterations precede or follow the fluctuation in symptoms in patients.

2. Differences between idiographic research and nomothetic approaches

The main difference between an idiographic and a nomothetic approach is that idiographic research aims to answer questions at an individual level (e.g. 'Does an increase in cortisol level predict deterioration of mood in this participant?'), whereas nomothetic research aims to answer questions at a group level (e.g. 'Do participants with low mood have higher cortisol levels?'). The statistical power of idiographic analysis is determined by the number of observations obtained for each individual, whereas the power in nomothetic research is determined by both the number of participants as the number of observations for each individual. While nomothetic research is possible with one observation for each individual, idiographic research requires as many observations as possible, as outlined in the next section ('Assumptions for performing idiographic analyses'). Further, it is good to note that some potential confounders in nomothetic research do not apply to idiographic research. Factors that are stable within persons during the measurement period (such as age and sex) do not need to be taken into account in idiographic research, since analyses are performed within individuals. Differences between nomothetic and idiographic research with regard to research questions, analytical differences, and practical issues are summarized in Table 1.

A discussion of the plethora of statistical techniques for nomothetic and idiographic research is beyond the scope of the current paper. We will only briefly address the differences between the idiographic and nomothetic approach. With nomothetic techniques, such as structural equation modeling, longitudinal data are processed at the group level to examine (bidirectional) relationships between variables. Nested subgroup analysis can be performed by applying different models on subgroups of patients, but analyses are, in contrast to idiographic research, not performed at the individual level. Multilevel structural equation models allow differentiating between within-subject and between-subject variances. Although the within-subject variance allows the level and strength of the association (i.e. the random intercept and the slope) to differ between individuals, individual estimates are generated posthoc, relative to group estimates, and no significance tests are provided for the individual estimates (Rovine and Lo, 2012). Moreover, assumptions are only tested at the group level and not at the individual level. Therefore, even multilevel structural equation modeling cannot define whether changes in neuroendocrinological factors predict symptom increases or vice versa for individual participants, which is possible with idiographic analyses, such as time-series analysis.

For further reading, we refer to standard introductory texts on time-series analyses (Chatfield, 2013; Durbin and Koopman, 2012), structural equation modeling (Bentler, 1980) and multilevel modeling (Hruschka et al., 2005), and to papers on techniques such as vector autoregressive modeling (Rosmalen et al., 2012), unified structural equation modelling (Gates et al., 2010; Kim et al., 2007), and convergent cross mapping (Sugihara et al., 2012).

3. Assumptions for performing idiographic analyses

Certain assumptions have to be met when performing time-series analyses. Most importantly, sufficient data points need to be available for each individual, since in time series analyses the number of observations gathered for each participant determines the statistical power to reveal an association. However, it is difficult to determine how many data points are exactly needed for time-series analyses. This is because the direction of the associations and the timing of lagged influences in the system under investigation are usually unknown and bidirectional and feedback effects can be present as well. For example, a decrease in cortisol level might lead to an increase in pain, while at the same time an increase in pain might lead to an increase in cortisol level. These influences can be modeled simultaneously in time-series models. Further, estimation of more parameters or non-linear associations decreases power and increases the number of data points needed (Brandt and Williams, 2006). Time-series analyses described in the context of the current how-to-paper are based on vector autoregressive models. These are linear models that can relate fluctuations in symptoms, such as depression, fatigue, and pain, to preceding or subsequent fluctuations in stress biomarkers. The required number of observations to yield enough statistical power depends, like in nomothetic research, on measurement error and the strength of the relationship between the studied variables. However, in contrast to nomothetic research, the measurement error and strength of association 'within' and not 'between' participants is important, and therefore the number of observations needed might differ between individuals. Simulation studies have shown that linear vector autoregressive models provide valid results with 30 time points, although larger numbers of observations yield more reliable results (Lütkepohl, 2007). Especially for stress biomarkers, which are normally influenced by many factors, larger numbers