



What is next for the neurobiology of temperament, personality and psychopathology?

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This paper represents the outcome of a multidisciplinary discussion on what works, what does not, and what can be improved, in ongoing work on biobehavioral taxonomies and their biomarkers. The authors of this paper, representing a wide spectrum of biobehavioral disciplines (clinical, developmental, differential psychology, neurophysiology, endocrinology, psychiatry, neurochemistry, and neurosciences), have contributed more extensive opinions to the Theme Issue 'Neurobiology of temperament, personality and psychopathology: what's next?'. The authors identified 10 directions in international and multidisciplinary cooperation, and multiple insights for 'what is next' for each of these directions.

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The long, multidisciplinary road to biobehavioural taxonomies

Temperament and personality traits are derived from *consistent behavioral patterns* (CBP) [1,2,10] that have been proposed to reflect a continua of symptoms in psychopathologies. Inherent consistency in these patterns should ensure success in their classification and in identification of their biomarkers. Such was the hope at the dawn of the 20th century — with the emergence of differential psychology, psychophysiological experiments on nervous system typology, biological and psychiatric theories of temperament, and typology of mental disorders within the International Classification of Diseases (ICD) and later the Diagnostic and Statistical Manual of Mental Disorders (DSM). The intense attempts to classify CBPs continued with the creation of lists of personality descriptors (20 000+), the blossoming of the lexical approach, several personality theories, neuroimaging, electroencephalography (EEG), psychophysiology, neurochemistry, 10 revisions of the ICD, and 5 revisions of DSM.

Nevertheless, a sober look at our current psychiatric and psychological taxonomies shows only modest progress. The more data that the biobehavioural sciences uncovered, the more it became clear that the subjects of the original CBP classifications — are transient, context-dependent, and complex [1,3–11]. It has taken several centuries for older natural sciences (e.g. physics, chemistry, biology, and medicine) to derive their taxonomies, through an ongoing, long history of trial and error, analytic discussions, comparisons of hypotheses and alternative models, and multidisciplinary cooperation. Much younger sciences, such as psychology and psychiatry, are set for a similar course.

The current Theme Issue attempts to spark a multidisciplinary debate on what works, what does not, and what can be improved in our work on taxonomies and biomarkers of CBP. The authors of this integrating paper represent a wide spectrum of biobehavioral disciplines (clinical, developmental, differential psychology, neurophysiology, endocrinology, psychiatry, neurochemistry, neurosciences, and genetics) and have contributed more extensive opinions to this Theme Issue. These opinions differ on several issues and so we have not attempted a consensus, but provide here a summary of what our experts agree on: fully, partially, or not at all.

Taxonomies need principles, and principles need theory

The history of other sciences with successful taxonomies highlights the importance of a theory with principles that at least provisionally explain the organization of patterns of interest, why and how certain classes are used. In chemistry, for example, the periodic table is validated by atomic theory; in biology, the classification of species is becoming standardized through genetics and phylogeny; and in medicine, bodily systems and illnesses have become codified through functional and dynamic principles from physiology and cellular biology.

With regard to CBP, several models have been proposed (e.g. Big Five, Big Six, Big Seven, RDoC, HiTOP, and FET [1,2,12,13,51]), some more heavily promoted by the American Psychological Association. However, the validity of their underlying principles is rarely discussed. In differential psychology and psychiatry, a few well-founded theories have been offered in an attempt to gain a unified representation of *the parabolic elephant* that is CBP [1,2,14–16]; however, clearly more explicit systematic work towards this is needed to derive a coherent, principle-driven theory [1,9,17].

Meanwhile, the principles of some taxonomic models amount to reiterating the psychometric requirements of test construction ('factor analysis said so'). CBPs are treated as output from a black box; without regard for the complexity of classify transient, context-dependent, biologically based systems — with nonlinear feedback relations between their components [1,10,18,19]. At most, the Big Five model might reflect universalities in social perception and societal regulation (promoting interaction, cooperation, information processing, rule-driven, and emotionally stable behavior) as expressed in natural language. The main arguments for the validity of this model are cross-cultural comparisons of groupings of language descriptors (i.e. sociocultural arguments), but not principles of neurophysiology. As Srivastava noted, the Big Five reflects principles of social perception and verbal-cultural processes, but not principles of

biologically based individual differences [12]. Moreover, recent studies show that the cross-cultural consistency of the Big Five model might be over-rated [20].

The HiTOP [13] and positive–negative affect models, in addition to factor analysis, use arbitrary bipolar concepts from clinical practice, not rooted in neuroscience, and the validity of these organizing principles is rarely scrutinized. The differences between these and alternative biomarker-based models, are almost never analyzed, even though experimental research using such alternative models began before the dominance of lexical models [11]. Principles of organization underlying these alternative models include the architecture of functional systems [15], EEG biomarkers [15]; the Pavlovian principles of properties of nervous systems [14,15,21,22]; neurochemical biomarkers [1,16,23], and a universal architecture of action construction and functional differentiation within neurochemical systems [1,2,23]. A more comprehensive list of models can be found in the Supplementary material of Ref. [24]. However, even this short list of alternatives suggests that these principles of biobehavioural taxonomies may be too diverse to assure a good convergence of models. Some authors suggest that a neuroscience-based taxonomy might be not possible (see Ref. [3]).

Therefore, a simple collection of CBP biomarkers may not be sufficient without identification of the principles organizing the complexity of these associations. The lack of coherence between several models and the justification of principles underlying these classifications leads to significant variability and incompatibility of interpretations of experimental variables and results. Meanwhile, labels and classes in taxonomies directly affect the ways in which hypotheses and research questions are shaped. Indeed, as Wacker and Paul point out, the situation is further complicated by the fact that even with seemingly simple behavioral data, several equally defensible alternative analytic paths exist that can lead to markedly different interpretations [9,25].

The vicissitudes of the human condition, such as adherence to ideology, dis/confirmation biases, use of ‘popularity’ argument instead of theoretical justification of models, and variations in expertise, require particular effort from professional associations and journals to counter their influence. Restricting literature reviews to specialized journals is unlikely to spark the multidisciplinary collaboration needed to accelerate progress in biobehavioural taxonomies. Expanding the analytic part of the task of developing CBP taxonomies, before experiments, could save resources in investigating CBP-biomarkers. This is especially important in neurochemical investigations that tend to be invasive and sacrifice many animals' lives when used animal models. [Tables 1](#)

and [2](#) list our insights about ‘What's next’ for biobehavioral taxonomies.

Biomarkers of consistent behavioral patterns are not just in the brain

There is a strong consensus among experts working on biobehavioral taxonomies that they should be based on biomarkers. Biomarkers of CBPs, however, should not be restricted solely to brain morphology and function. Here are a few arguments to support this statement, with suggestions for ‘what's next’ in the [Table 1](#):

A) Neuroimaging, so far, has low reliability and low replicability of associations between specific brain structures and specific CBPs [9,4,26,27]. The observed activation of brain structures might be associated with functions of behavioral regulation that are not part of the experimental design of a given study, and this could generate false attributions for the biomarkers. The same brain structure is often implicated in multiple, very different CBPs [8]. For example, the ventral striatum reportedly is activated in association with positive affect and reward processing [28,29], negative affect [30], aggression, [8,31], alcohol misuse [32], social rejection [27], extraversion (E) [33] and the generation of the program of actions and habits regardless of emotional valence [2,34]. Similar incompatibility of overlaps in CBP-biomarkers associated with neuroimaging were observed for other brain structures, especially the amygdala, medial frontal lobes, and cerebellum. These overlaps might, of course, suggest the existence of a common behavioral denominator behind these CBPs (e.g. preparation and anticipation of actions) and likely ‘ensemble’ interactions between brain structures. However, the nature of regional activation/involvement may well vary across CBPs [11,29] (see also B, below).

B) The differential involvement of brain structures in specific aspects of actions and contexts is thought to be due to differences in the neurochemistry of their innervation [1,2,7,8,23,24,29,35–39,43–45]. Neurochemical systems include neurotransmitters (serotonin, dopamine, noradrenaline, acetylcholine, GABA, and glutamate), neuropeptides including hormones and opioid peptides, and a spectrum of their receptors, transponders, transcription factors and other mediators. These neurochemical processes should be a focus in the search for biomarkers as much as the neuroimaging of well-identified brain structures [1,2,7,8,23,24,35,37–39]. The resource intensive nature of neurochemical studies does create significant obstacles for these studies. Moreover, neurochemical systems often act nonlocally via extracellular ‘volume transmission’ [40], questioning the validity of approaches that are strictly structure- or network oriented. The diffuse nature of neurochemical processes presents a great methodological challenge in studying

Table 1

'What's Next' is needed for organizing and 'continua' principles in CBP taxonomie.

'What'	'How' for directions of analytic work	'How' for directions in research setups and measurement
Organizing principles of taxonomies	<ul style="list-style-type: none"> • Round tables between representatives of opposing theories of the organizing principles for taxonomies. 	<ul style="list-style-type: none"> • An organized discussion of potential multimodal/multimarker research setups where not one but several biomarkers (either several brain areas, neurotransmitter systems or gut-brain interactions) are investigated [2,5,4,8,17,36,41,56] using various statistical approaches ([5,10,37]).
Outlining hypotheses for CBP-biomarker associations	<ul style="list-style-type: none"> • Creation of special sections in peer-reviewed journals for 'competing hypotheses' of CBP-biomarker associations with side-by-side publications of opponents' and/or joint (between opponents) articles. • Requirement for alternative models and hypotheses to generate predictions instead of merely exploratory gathering of associations [9], and to explain outliers and negative results. 	<ul style="list-style-type: none"> • Organization of an online platform using interactive technology similar to Wikipedia and ArXiv, where alternative hypotheses are debated (with proposed name 'Socrates', to underline the analytic, debate-oriented nature of this project).
Attention to biomarkers beyond brain structures/beyond neuroimaging	<ul style="list-style-type: none"> • Division of the current Task Force (RDoC) [51] into 'topical' streams (i.e. groups focused on either neuroimaging, or neurochemistry, or gut microbiota or neuroimmunology) and 'bridging' streams integrating the topical findings. • Advanced Study Institutes (summer schools) for specialists from different biobehavioural sciences to teach each other most modern knowledge in their fields, and facilitate future multidisciplinary projects. 	<ul style="list-style-type: none"> • Transparency of the work on taxonomies to the wide academic community with possible involvement of alternative multidisciplinary teams (using proposed platforms of Socrates and Hippocrates), instead of keeping the creative process within 'closed clubs' of chosen scientists. • More prominent courses teaching neuroscience and measurement theory in psychology programs. • An international project (online platform) focused on 'fluid' CBP biomarkers (neurochemical, endocrine, microbiota, and psycho-immune), with proposed name 'Hippocrates', honoring the author of the idea of biochemical origin of temperament. This platform could facilitate work on hypotheses, setups and coordination of research, funds raising and data exchange [1,41]. • Genetic studies [8] of temperament traits since these traits represent neurochemically based regulation of behavior [1,23,35-37,62,81] • Calls, with awards, for new insights into possible creative methodologies for noninvasive neurochemical research. • Multidisciplinary bridging using highly educated 'scientific interpreters' who would adopt/translate knowledge between disciplines; more welcoming environment for 'specialists-outsiders' coming from different disciplines.
Accommodation of the concepts of clinical and ontogenetic continua in taxonomies	<ul style="list-style-type: none"> • A topical Task Force offering new formalisms to handle the clinical-health and ontogenetic continua and CBP transitions along these continua. • Organization of round tables, Theme Issues of peer-reviewed journals and discussions of offered formalisms (e.g. functional constructivism) [1,2,5,10]. 	<ul style="list-style-type: none"> • Applying the same setups across clinical versus healthy samples matched by age and sex [4]. • Multigenerational cohort studies allowing natural experiments [56,77]. • Formal, evidence-based structuring of information about professional and personal histories, consistent elements of everyday functioning (using reliable sources and not retrospective recall) to be incorporated into diagnostic criteria and assessment tools. • Investigations of the role of maternal psychophysiology on infant CBPs [7,56]

core biomarkers of CBPs. Neurochemical models of temperament [1,2,16,23,24,39] give a chance to explore the contribution of molecular genetics to consistent dynamical features of behavior [36].

C) Modern 'gut psychiatry', endocrinology, and neuroimmunology have demonstrated that some biomarkers of CBP maybe outside the brain [2,39,41,42,46]. Gut microbiota [41,42,46], immune and hormonal systems

Table 2

'What's Next' related to contextuality, interspecies comparisons and conceptual parsing in CBP taxonomie.

'What'	'How' for analytic work	'How' for directions in research setups and measurement
Consideration of interspecies continuum to improve studies using animal models	Evolutionary analysis and integration of animal (translational) studies to validate the organizing principles of CBP taxonomies including functional ecology of the tasks/contexts comparable between studied species.	<ul style="list-style-type: none"> • In human studies, dividing 'socio-cultural' variables into 'socio-interactive', 'probabilistic' and 'cultural', to improve compatibility with animal studies of sociointeractive (predator-prey, child-parent, dominance, and group dynamics) and probabilistic (novelty and uncertainty) aspects of CBP (Figure 2). • Animal studies with behavioral tasks compatible with human temperament models to study culture-independent aspects of behavior [7,10,61,76]
Addressing the problem of significant context-induced variability of CBPs (Figure 1)	<ul style="list-style-type: none"> • A topical Task Force on taxonomy/typology of contexts, with organization of round tables and Theme Issues of scientific journals. • Classification of the degree of individual's involvement, dependence on and access to informational and provisional resources, and to social-cultural infrastructure. 	<ul style="list-style-type: none"> • Multiregional international research project enabling comparisons of the impact of environmental biochemical factors (climates, diets, exposure to toxins, and psychostimulants), probabilistic (e.g. uncertainty, forced changes inducing stress), sociointeractive and cultural factors contributing to CBPs. • A call for new formalisms and measurement approaches accommodating behavioral variability as a function of context [1,2,5,10]. • Continuous psychophysiological tracking for periods of time instead of single experimental measurements, to study interactions between CBP, consistent environmental and situational factors in everyday behavior
A conceptual decluttering of specific CBP concepts and measures	<ul style="list-style-type: none"> • Addressing jingle-jangle fallacies in CBP concepts and associated assessment measures • Sorting out the conceptual disagreements among temperament and bio-personality researchers using a possible Socrates platform 	<ul style="list-style-type: none"> • Resolving conceptual disagreements among temperament and biopersonality researchers related to: a) whether or not N and E should be called temperament traits (as described originally) or personality traits (as referred in trait-personality psychology); b) can biopersonality group be integrated with temperament group? c) what is CBP consistency in light of brain plasticity under environmental (including cultural) factors? d) what is the best setup for a study that would delineate temperament and personality traits?
Statistical and/or mathematical approaches	<ul style="list-style-type: none"> • Organization of 'reflections' round tables and journal Theme Issues systematically reviewing new or recent mathematical, statistical and measurement approaches, to make progress in this area more visible. • Calls for new formalisms, statistical or mathematical approaches for multimarker interactions. 	<ul style="list-style-type: none"> • In psychometrics, giving more weights to neuroscience-based justifications of the psychological measurement tools rather than to FA results. • Delineation of biomarkers that capture the modulatory effects of <i>continuous</i> changes in stimulus intensity/difficulty rather than binary (<i>contrast</i>) conditions [4] • Use of larger cohorts with independent samples [8,9,56] to ensure sufficient power, critical reflection of the collected measures, a more stringent testing • Evidence-based quantification and standardization of questions regarding individual's functioning in observer-based measures (e.g. parents to assess children, family members to assess elderly or disabled) [21,56] • Development of behavioral and quantitative methods [27,37,78]

[7,39,41,46–49] impact many aspects of behavior, with emotional regulation as the most explicit example. Moreover, other psychophysiological and biological processes — physical touch [7], genes [21,33,50] (Online

Etymology Dictionary, <https://www.etymonline.com/word/personality>, retrieved December 2021), sunlight, diets, hormones response to perceived social support — were reported as making significant contributions to

CBPs and indeed interact with enteric, immune and endocrinological systems to impact central nervous system function and CBP [41].

The structure of biobehavioural taxonomies should accommodate the concept of a dynamical continuum

One important challenge for the development of biobehavioural taxonomies is that CBPs do not have strict boundaries in their properties. Instead, individually CBPs possess a dynamic, 'fuzzy' rather than static nature, reflected in current psychiatric taxonomies [1,2,5,10]. For example, DSM-5 includes specific time frames for the onset and periodicity of symptoms to make specific diagnoses. Current taxonomies, however, do not accommodate the fact that CBP can transit between several existing taxonomic categories. For example, people with post-traumatic stress (PTSD) often (but not always) have co-occurring major depression (MDD); neuroticism (N) and sensation seeking are not necessarily mutually exclusive, and neither are psychopathy and empathy [39,52,53]. CBPs, therefore, could be presented *along multidimensional continua (spectra)* of the following types:

Clinical-health continua

The degree of behavioral deviations from severe to mild symptoms of psychopathology, and those that might or might not be seen as clinical symptoms and healthy temperaments [1,2,5,6,10,13,16,19,33,53,54]. The classification of diagnoses as a function of severity is often difficult since severity fluctuates with time. There is also overlap, co-occurrence, comorbidity and phenomenological heterogeneity among diagnoses [4–6,10] and the behavioral expression of normative temperament and personality traits. The application of label-oriented and category-oriented approaches to biobehavioural taxonomies, common in the early 20th century, showed that these approaches are not flexible enough to deal with the dynamics and the fuzzy boundaries between health and psychopathology [6,54,55]. This led to the development of the dimensional and constructivism approaches [1,2,13,54].

Ontogenetic continua

There are well-documented age-related changes in neurophysiological, neuroanatomic and hormonal systems of behavioral regulation, making all age stages neurobiologically unique [5,27,35,41,56,77,88] (Online Etymology Dictionary, <https://www.etymonline.com/word/personality>, retrieved December 2021). Maturation of biological systems (e.g. brain function) is seldom linear and varies as a function of sex [57–59]. The same individuals, as they age, change their values, interests, attitudes, etc. (i.e. essential components of personality). Through development, some aspects of CBP and symptoms of psychopathology are more transient, whilst

others remain more stable [60]. Yet, relative to their peers, there are CBPs that distinguish one person from another, and there is continuity within each individual despite these age-related transformations. Even for individuals who exhibit comparable levels of specific traits at baseline, the longitudinal trajectories of these traits can vary markedly [5,56] (Online Etymology Dictionary, <https://www.etymonline.com/word/personality>, retrieved December 2021). Several studies found inconsistencies in associations between specific traits and the activation of brain structures in samples using children and adolescents [8,27], and in samples comparing adults and adolescents [27], illustrating the importance of considering brain maturation when understanding biomarkers of CBPs. Genetic factors vary in expression as a function of age [7,88] (Online Etymology Dictionary, <https://www.etymonline.com/word/personality>, retrieved December 2021), as do parenting and peer interaction factors [7,27,77]. Moreover, epigenetic stress and nutrition have been shown to impact *in utero* development, moderated by their time of onset [7,56].

Intraindividual variability within consistent behavioral patterns

Observed when the same people give variable responses to similar situations or in performing the same task. Such variability is often attributed to changes in context: indeed, by modeling trial-by-trial data, studies have demonstrated that both animals and humans dynamically adjust their representation of value to fluctuations in the context [5]. However, within-individual variability in behavior [1,4,7,19], neuroimaging patterns [4,5] and neurochemical responses [1,8,35,38] exists even when the context (such as experimental conditions) and age are relatively constant. This problem of variability was identified back in the 1930s by Bernstein as a degrees of freedom problem. He proposed that no single act is repeated twice, rather it is constructed anew [62]. This creates a methodological and analytic challenge in mapping the correlates of specific CBPs [1,4,5,7,10,11]. Intraindividual variability diminishes the value of the 'contrast' approach that compares only two contrasting conditions (e.g. one control and one experimental) [4]. Moreover, it is typical that some of the intraindividual variability in behavior is handled in research by excluding outlier observations. Ideally, the principles of a good taxonomic system should be able to explain outliers. This attention to outliers, is in fact, how the principles underlying models are tested in mature sciences.

Interspecies continua

Similarities and differences in the ranges of CBP in humans as compared to other animals enable research in translational psychiatry, psychology, and psychopharmacology [7,61,76]. A lesson learned from comparative, ecological, and evolutionary branches of psychology over the past century is that a direct analogy

of external behavior between species is not always applicable. For example, communication is not always vocal in various species, and biting and roaring are not always signs of aggression. Yet, there is great potential in studying biomarkers and typology of consistent biobehavioral differences using animals [76] because there are strong genetic similarities between humans and other species, as well as similarities in the main aspects of functioning. Non-human animals can be used to model autism, schizotypy, attention deficit disorder, and stress–resilience [76]. Animal studies appear to be especially useful for invasive neurochemical investigations (which are not allowed in humans) of the action of psychostimulants, drugs, physical and social stress on mother's physiology and of the impact of altered maternal behavior on infants [7,8,58,61]. However, important differences between humans and animal models exist in the maturation and capacity of many 'higher-order' neurocognitive functions (e.g. executive, moral, and self-referential domains).

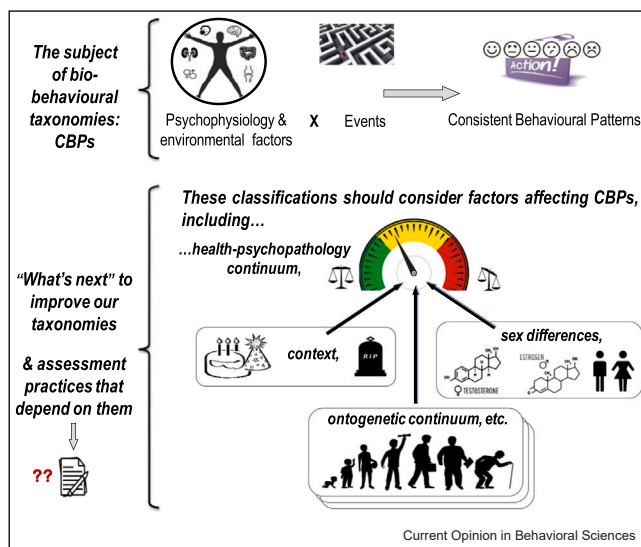
Situational variability (context) should be a part of consistent behavioral patterns taxonomies

The differential responsiveness of the same individual to different contexts is a well-documented phenomenon [3,10,19,37,78] (Figure 1). The diversity of personal life histories alters responses to the same context in different people and the responsiveness to different contexts in

the same individual. These differences have psychophysiological bases, so they should not be ignored. For instance, stress induces changes in the immune system, such as raised inflammation that has been associated with individual differences in CBP (e.g. impaired cognitive empathy) [46]. Also, traditionally testosterone is associated with the propensity for aggressive behavior [48], whilst oxytocin is proposed to decrease aggression [49]. However, testosterone has also been associated with prosocial behavior, and may rather reflect a need to obtain social dominance — thus, its effects are differentially manifest depending on context [39,47]. Also, in specific contexts, such as following provocation or in response to an 'out-group', oxytocin may increase aggression (briefly reviewed in Refs. [8,39]), especially in mothers protecting their young [39]. This might be understood as a role of oxytocin in facilitating accurate discrimination of threat [41], which is context dependent. Context dependency in CBP is present even prior to the impact of life experience. This is seen in the ability of infants to show jealousy, and in differential attachment patterns which depend on the context of caregiver relationships, documented with distinct neuronal biomarkers [7].

It is not a trivial task, therefore, to accommodate a typology of contexts or to choose 'general and universal' experimental methods to study CBPs that could be applicable to the interpretation of individual differences in these contexts [1,3,4,10] (Table 2). Types of possible contexts go far beyond the short lists of conventional experimental contexts, such as stress conditions, social support, and affiliations. For a given CBP, there should be a theory of the specific context features that are relevant with regard to moderating (and mediating) the expression of this trait [3]. The concept of specialized extended phenotypes might be useful in this line of analysis [1,2]. Moreover, evolutionary aspects are fundamental to the mechanisms of behavioral regulation, and so analysis of context should include systemic, evolutionary tendencies affecting CBP and their biomarkers [7,61,76].

Figure 1



Biobehavioural classifications should accommodate principles described in this paper, among which are clinical and ontogenetic continua; sex differences and context dependence (black arrows symbolize the affect of these factors on psychological measurement). The structure of DSM/ICD and many personality and temperament models, however, do not accommodate these principles, and this affects assessment tools and assessment outcomes.

Sex differences should be accommodated in the structure of taxonomies

Research over the past century demonstrated numerous sex differences in CBPs and their associations with biomarkers, both quantitative and qualitative [7,8,36,39,41,57–59,63,64]. While science has recently begun to acknowledge that sex/gender is not a binary concept, previous research mostly investigated differences with regard to the traditional concepts of male versus female sex. For example, hippocampal volume predicted parent-reported aggression in healthy adolescents, but only in females (reviewed in Ref. [8]), whereas dysregulation in the MAO-A allele —

amygdala-vmPFC coupling predicted increased harm avoidance and decreased reward dependence, but only in males (reviewed in Ref. [36]). Sex differences were also found in the impact of prenatal maternal antidepressant use on infant temperament; dampened reactivity in infant girls, heightened activity in boys (but a decline in distress to limitations) (reviewed in Ref. [7]). In adult samples, positive correlations between E and the ratio of gray to white matter volume in the left hemisphere, or between N, E, and conscientiousness and gray matter volume were only detectable in males, but not in females (reviewed in Ref. [36]). The analysis of sex-specific correlations is often exploratory (and sometimes tested and reported as if they were confirmatory). Reduction in *p*-hacking and promotion of confirmatory research in this domain might be facilitated by explicitly accommodating sex differences in current models.

Moreover, a binary division of sex groups appeared to be inadequate [63] and not reflect the diversity of sex as a construct reflecting sex-hormonal balance and related sexual needs. The interaction of sex with cultural standards emerges as gender, and this decouples sex-related variables affecting CBPs (Figure 2): biomarkers (hormonal systems), their interactions with physical factors, sociointeractive factors (such as mating, competition, dominance, possible to study on animal models) and impact of cultural factors, including sex-gender interaction in humans.

CBP taxonomies should, therefore, include a consideration of sex differences (Figure 1) and their interactions with three types of environments depicted in Figure 2.

Language biases and conflation disrupt terminology and require regular conceptual decluttering

Jingle-jangle fallacies and language biases

When psychiatry and psychology emerged as sciences at the end of the 19th century, people viewed them as largely 'talking and observing' professions, promoting reliance on verbal descriptors. The generation and manipulation of new jargon related to specific CBPs felt natural, even though there were calls for behavioral, experimental and biomarker justifications of emerging concepts.

In multiple revisions of psychiatric taxonomies, decisions on deleting, unifying or separating categories (as happened for depression, schizophrenia and OCD) were based on the opinions of clinicians operating by verbal descriptors, not on neuroscience that would demonstrate a need for such unification or separation. A hard lesson learned from these revisions was that special care should

be given to the way that we use language, including naming and defining variables.

The first price that psychology and psychiatry paid for ignoring linguistic biases and arbitrary naming of behavioral patterns is the labels overlap problem, or, as pointed by Brandt and Mueller, 'jingle-jangle fallacies' [3,65,66]. These include the faulty assumption that two different things are the same because they have the same labels (jingle fallacy) or that two (almost) identical things are different because they have different labels (jangle fallacy). Non-clinical examples include:

- the meaning of CBP E was transformed from the original temperament trait described by Jung as a type of behavioral orientation (to other people's influence) to Eysenck's interpretation of E as insufficient cognitive arousal forcing people to seek out stimulation (e.g. socialize), to Gray's interpretation as stronger Behavioral Activation over Behavioral Inhibition, currently coming to the mix of the concept of general arousal (following Gray, Cattell, Norman and McCrae's interpretation), plus positive affect and appetitive motivational systems [18,38,29]. In other words, E now has a meaning, which is almost opposite to that which Jung intended, and an inheritance of multiple interpretations in various models. Thus, several neurochemical hypotheses of E have been proposed that vary in their definition of E [2,14,29,38];
- partial overlaps exist between the concepts and measuring scales of sensation-seeking, novelty-seeking, reward-seeking or reward-dependence [16,39];
- empathy concept referring to both the representation of intentions/knowledge of others ['Theory of Mind'] and emotional responsiveness to the distress of others;
- overlapping functional processes referred to 'trait anger' and 'irritability';
- the concept of 'emotionality', which, despite its common use, is still defined circularly ('emotionality is how people express and feel their emotions'); and is known for having multiple components, biomarkers and conflicting theories [24,39];
- the mix-up between concepts of 'temperament' and 'personality' as described below, which were also conflated with the concept of character [16], (Supplement in Ref. [24]), [67].

Second, trust that common language objectively reflects consistent biobehavioural differences (known as Allport's lexical hypothesis) still exists among the followers of the lexical approach even though the past century uncovered several language-related biases (see Supplement in Ref. [84]). These include a bipolarity of human verbal descriptors [69], a sociability bias of language, a proregulatory bias of language, emotionality and embodiment biases in cognition, and so on ([84]; see

Figure 2

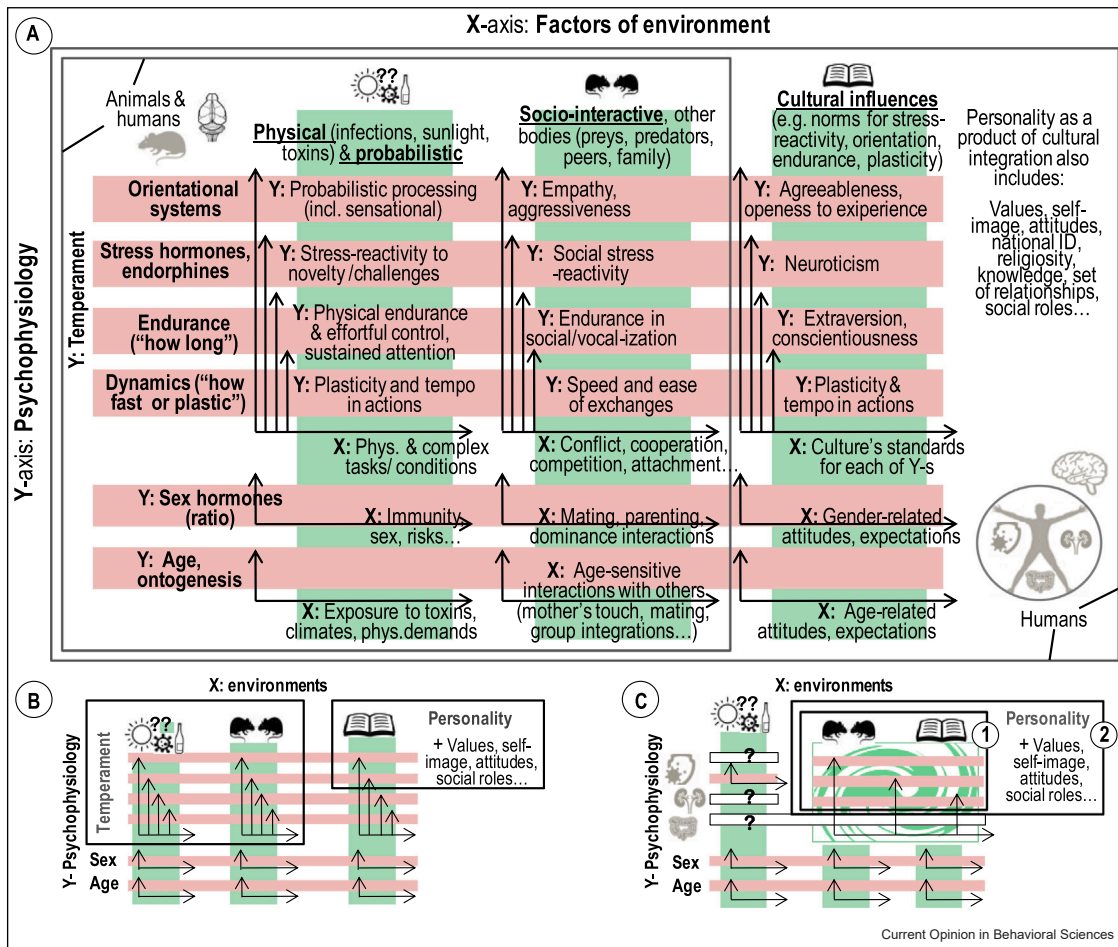


Illustration of different approaches to the definitions of temperament and personality and the use of these concepts to study associations between different types of environment (axis X, named in part (a) and depicted graphically in parts (b) and (c)) and three concepts reflecting psychophysiological systems (axis Y). To save space, physical and probabilistic factors of environment are grouped in one column, and the grouping of temperament or personality traits do not follow any particular model. Some models, for example, consider N (emotionality) as part of orientation [1,2,15] whereas others as a trait independent from orientation (for a comparison of temperament models see Supplement in Ref. [24]). (a) A separation between socio-interactive and cultural factors of environment shows its benefits not just for sex and age studies but also in studies of temperament and personality. Rectangular shapes show the overlap and differences in X*Y processes in behavior of animals and humans. The overlap opens perspectives for translational (animal) studies applicable for interpretation in humans, with careful consideration of functional ecology of studied animals. (b) Temperament researchers' and (c) two personality researchers' views on the division between the concepts of temperament and personality marked by rectangular shapes. Both personality approaches do not differentiate between socio-interactive and cultural factors, overlap E and N personality traits with temperament traits of sociability and emotional reactivity and do not consider traits related to dynamics of behavior (such as plasticity) as part of personality. Bio-personality view (c-1), in contrast to classic personality view (c-2) also does not include a list of characteristics in the last column (values... social roles) in personality. See Section *Language biases and conflation disrupt terminology and require regular conceptual decluttering* for details. Yet, temperament traits related to endurance, plasticity and stress reactivity in actions could be measured directly in behavior and differentiate between healthy and clinical CBPs [1,2,53] and so should be a part of biobehavioural taxonomies. X*Y graphs: more detailed presentation of parameters in temperament models allows more detailed and differentiated investigation of interaction between individual's psychophysiology and environments.

Ref. [18] for review). Language biases arise from the fact that a language is a society's tool to ensure (among other things): human interaction, cooperation, information processing, rule-driven, and emotionally stable behavior. Whereas these five prosocial functions of human language do not constitute the full list of these functions, due to their universality they influence the outcomes of

the Big Five model of personality as the result of its lexical nature. Cross-cultural comparisons using this model, therefore, reflect universalities in verbal biases related to societies' needs. For good reasons, biological sciences do not verify their taxonomies based upon the cross-cultural consistency of opinions but use biomarker-based arguments [10,17,18].

Third, bipolarity of human perception [69] can affect the way how we name clinical categories (positive–negative, external–internal, and clinical–healthy) and perceive even the most abstract concepts [84]. Meanwhile, psychophysiological systems induce a range of expression of every CBP. Moreover, as Blair and colleagues note, it became traditional to contrast control and experimental groups (also a sign of bipolarity in methodology) and interpret the observed results as showing the effects of experimental conditions [4,5].

Fourth, common language does not differentiate between descriptors related to CBPs with well-identified biomarkers (e.g. tempo, or speed of actions) and ‘component’, heterogeneous CBPs, that are likely the product of several more basic symptoms, whether in psychopathology (e.g. PTSD [21]; psychosis [5,68], schizotypy [5,27,70], narcissism [27], aggression [8,31,48,49,71], MDD [46,53,60], and Generalized or Social Anxiety [53,56,79]), or in healthy CBPs (such as E [14,23,33], or emotionality [3,14,24,39,77]).

Hierarchical models attempt to accommodate a multi-component approach to such ‘mixed’ CBP, assigning strict associations of specific CBPs (‘facets’) to overarching categories (‘factors’). This strict division of CBPs into categorical boxes generates multiple disagreements: for example, HiTOP uses classes of ‘internalizing’ and ‘externalizing’ disorders but does not include thought disorders to the internalizing class, detachment to the externalizing class and views (very different in etiology) symptoms of MDD, PTSD and generalized anxiety as one class of ‘Distress’ disorders [13]. As a nonclinical example, E, as noted above, was historically associated with multiple CBPs, often explained by the concepts of general arousal and positive affectivity. Analysis of neurochemical biomarkers of several behavioral aspects attributed to E showed that these aspects are based on different neurochemical ensembles and so require distinct concepts, to trace the CBP–biomarker associations [1,2,23,24,39].

Jingle-jangle fallacies related to concepts of ‘environments’

A division of factors contributing to CBP into biological versus sociocultural seems insufficient as both within-body and within-environment systems are of biological nature, and interactive and cultural factors induce neurobiological adjustments. The division of factors to within body and environment related is also not without flaws but at least it allows more informative setup of studies. There is, however, a conflation of several types of environments into one label of ‘environment’, resembling jingle fallacy, as well as inconsistencies on how variables of environment could be partitioned, resembling jangle fallacy. Some researchers blend social interactions and cultural standards, but there are benefits

in conceptually differentiating social environments (interactions with others — parents, peers, mates, competitors, prey, and predators, common in animals) from cultural environments (behavioral standards, values, and knowledge). Moreover, factors of the physical environment influence the neurophysiology of behavior and can contribute to CBPs. The example of COVID-19 showed that factors in the physical environment (infection) can affect people's endurance and ability to focus (i.e. temperament traits) when people contracted COVID and increases anxiety after that (i.e. induces psychopathology), and there is not much that cultural factors can do about it [72]. Physical factors regulating CBPs depicted in Figure 2a can also include the amount of sunlight as it determines the release of hypothalamic orexins and so behavioral arousal [23], diets [43–45] and the use of common psychostimulants (alcohol and tobacco).

Finally, probabilistic aspects of environments (such as novelty of events, probability of positive and negative events, estimated in/capacities to handle events (as a stress factor), commonalities, and exceptions in events and object features) could be separated into different variables from cultural, sociointeractive, and physical factors of environments. Probabilistic challenges exist in behavior of both humans and animals, and so possible to classify in translational and longitudinal studies and as conceptually different from cultural factors.

As a jangle fallacy, the way in which variables of environment could be partitioned, are inconsistent among researchers (see Section *Mathematics and psychometrics are the tools but not the leading advisers for taxonomic principles and biomarkers* and Figure 2). Cultural training in humans leads to the development of nonbiological but still consistent elements of CBPs, such as values, attitudes, national ID, religiosity, knowledge, self-image, sets of relationships, and social roles. Many view these as traditional parts of personality, but others do not (see Section *Mathematics and psychometrics are the tools but not the leading advisers for taxonomic principles and biomarkers*). In fact, the word ‘personality’ came from the Latin word ‘*persona*’, a mask worn by an actor to represent a character in a social performance (Online Etymology Dictionary, <https://www.etymonline.com/word/personality>, retrieved December 2021). These cultural components of personality make the personality concept difficult to apply to animal models or pre-cultural children.

As Figure 2 illustrates, separating physical, probabilistic, sociointeractive and cultural environments helps to identify psychophysiology–environment interactions (depicted as axes X and Y) for sex and age in a carefully differentiated and informative way (some described in this Theme Issue [7,35,56,77] see also [50,57,72,73]). The same can be done for the separation of CBP

biomarkers in their interaction with different environmental factors, as some researchers show [74,75]. The jingle-jangle fallacies of the concepts of physical, social-interactive, and cultural environments happened probably because at the observation level, cultural impact is delivered through social interactions using physical objects and in physical environments. Delineating entangled types of environments (Figure 2a) would be similar to the approach in medicine, analytically distinguishing between cardiovascular, respiratory and endocrine systems, even though these systems are entangled in every single act.

Jingle-jangle fallacies related to concepts of 'temperament' and 'personality'

The most controversial 'blending' of concepts that has triggered intense discussion among the authors of this Issue relates to the concept of temperament, which is often conflated with the concept of personality. There are different views on the distinction between these terms, though all agree that sociocultural factors interact with neurophysiological systems of behavioral regulation (Figure 2). Some authors propose that phylogenetic and ontogenetic development of brain systems (such as those that allow higher order domain processing of sociocultural, executive, moral, and self-referential information) should be used to differentiate temperament and personality [2,18,41]. An analogy might be with temperament as an ever-growing trunk in a tree, whilst personality represents the diversity of branches that grow in different directions depending on the weather (i.e. sociocultural environment). The differences between approaches stem partially from the different historic traditions in the definitions of these concepts: these differences mainly developed after the occurrence of bioperonality psychology and lexical approach in the mid-20th century. Views on the distinction between temperament and personality could be divided into the following groups:

- 1) The 'common temperament theory' (Figure 2a and b) defines temperament as consistent biologically based individual differences in behavior that a) are observed in precultural individuals (animals and infants), b) emerge from the beginning of life and observable before cultural training; c) are relatively consistent across life; d) relate to formal dynamic and not content aspects of actions; and e) are spontaneous, often not included in self-image [15,18,21–24,35,77]. The traits of E (described by Jung) and N (described by Kagan [73]) were identified as temperament traits before their use in personality models [2,6,14, 21–24,35,37, 41,56,73,76,77,80]. They indeed showed the highest associations with biomarkers even when these traits were called 'personality traits' [29,37,41,81], including in studies on animals [82,83]. This approach also consistently points to the distinct association of temperament with formal *dynamical*

aspects of behavior: endurance, speed of actions, ability for sustained attention, plasticity, stress reactivity/resilience, impulsivity, speed in learning [1,2,15,18,21,22,35]. Dynamical aspects of temperament (distinguished from 'content' of behavior, that is, motives, social roles, and attitudes) were identified in differential psychophysiology experiments on adult temperament conducted in Russia and Poland for decades during the 20th century [6,10,15,18,21–23, 35,73,80]. Temperament researchers also point to the benefits of distinguishing this concept from personality since it allows temperament traits to be studied using animal models, following a long tradition of using the 'temperament' concept in animal breeding and farming practices. Moreover, even in humans, consistent individual differences in the dynamical properties of CBPs, dispositional moods, stress resilience and behavioral orientation to mechanical or social objects, are present in very early childhood, long before cultural standards and knowledge are internalized by an individual, and thereafter during the individual's life. Temperament researchers point out that there are cultural standards and other environmental demands for dynamical (endurance, plasticity, and tempo), orientational aspects (sensation seeking, empathy, and probabilistic processing), and emotional reactivity of CBPs (Figure 2a). Temperament traits related to these aspects of behavior interact with these demands, but the individual differences in these traits still remain, despite training and cultural disciplining. In this sense, interactive transformations with environments emerge as neurobiological adjustments, for example, to stress or cultural training but individual differences in the listed aspects of temperament remain consistent in diversity of settings. Figure 2 lists some but not all temperament traits (see Refs. [1,2] for a more complete model and Supplement for [24] comparisons of main models).

- 2) The 'classic temperament approach' (not shown in Figure 2) includes the common temperament theory, but also draws inspiration from the original concept of 'temperamentum' (as a mixture of biochemical fluids in the body), proposed by Hippocrates and Galen. This approach points to the contribution of neurochemical brain and body systems, immune, endocrine and gut microbiota systems [1,2,8,23,24,35–39,41–46] in CBPs. This approach differs from the first one only by the emphasis on neurochemical, neuroendocrine, neuroimmune, and gut biota biomarkers of temperament. It suggests that neuroimaging should be combined with analysis of these biomarkers because different functionalities of brain areas could be linked to their different neurochemical compositions [2,16,24,35,39]. Having a neurochemical mapping of brain structures and a neurochemical model of temperament and psychopathology [1,2,14,16,23,24,29, 39,53] (with the Functional Ensemble of

Temperament model, as example [1,2,23,24,39]) opens up the possibility of tracing interactions between biomarkers of CBPs and physical environments.

- 3) 'Bio-personality' psychology focuses on the individual differences that two abovementioned approaches call temperament but suggests that, while doing so noisily, modern personality scales can reflect such differences just as well as temperament scales do. This approach has emerged in mid-1950s when Eysenck offered a model, which called E and N temperament traits as 'biologically-based personality traits'. Such an overlap of biopersonality traits with temperament traits continued when empathy and sensation seeking traits were identified in animals and were linked to specific biomarkers. This approach does not differentiate between socio-interactive (common in animals) and cultural factors (not present in animals) of environments (Figure 2c1), or between dynamical and content-related aspects of CBPs. It also does not differentiate between temperament and personality traits on the basis of the argument that in humans, temperament interacts with culture and becomes personality [18]. When the E and N temperament traits were observed in apes and monkeys, this approach attributed it to biopersonality traits, as components of the 'Big Five' [82,83]. Moreover, this approach does not emphasize components of personality that depend on the cultural environment (values, attitudes, etc. — listed in the last right column of Figure 2a; and as depicted in Figure 2c1).
- 4) 'Classic differential psychology' (Figure 2c2) considers personality as a broader concept, in comparison to the third approach and includes culturally determined aspects of CBP that make the behavior of an individual consistent. These aspects include but not limited to: values, attitudes, national ID, religiosity, knowledge, self-image, set of relationships, and social roles.
- 5) The 'lexical approach' started as a collection of all descriptors of behavioral individual differences by Allport, but the original list of these descriptors was arbitrarily reduced by removing 95%. The remaining 5% includes descriptors related to temperament (N and E), elements of cognition (as Openness to Experience in Big Five model), and traits affected by cultural standards (Figure 2c2). In the past 20 years, Big Five researchers moved to studies of biomarkers associated with components of their models drifting closer to the third, biopersonality approach (Figure 2c1). Investigations using these lexically derived models have contributed significantly to our knowledge of the universality of social perception [11,20,84], but progress in biobehavioural taxonomies will remain slow and unproductive if we continue

relying on social perception to classify biobehavioural systems.

- 6) The 'clinical approach' still uses the concept of personality in the names of the tests that have scales related to clinical diagnoses (e.g. as in the MMPI, 16PF, and CPI).

The concept of personality has, therefore, had multiple interpretations, and focused discussions on its content, including its differentiation from the concept of temperament are needed, especially in relation to the overlaps of E and N in both concepts. The arguments between temperament and biopersonality researchers also arise around the question of whether or not temperament traits could be observed, measured and separated from personality traits in humans who have a history of cultural integration of their biologically based differences. Temperament researchers suggest that cultural standards produce behavioral strategies to meet these standards, but the individual differences in dynamical features of CBPs (e.g. endurance, plasticity or emotional reactivity) remain and constitute temperament traits. In fact, a dozen temperament traits appear to be identifiable by proper measurements ([15,53,73], see Supplement in Ref. [24] for comparisons of temperament models), but development of behavioral methods is needed. Some studies showed that personality traits could be based on combinations of temperament traits [80], and temperament traits of endurance, tempo and N differentially impact the way how people attribute meaning to cultural constructs [84].

Moreover, there is a disagreement between these approaches on the degree, to which culture can change temperament and personality traits. Temperament researchers point to consistent individual differences in individuals exposed to the same cultural influences or stresses, and biopersonality researchers point to brain plasticity in response to cultural influences. Development of compensatory behavioral strategies under these influences decreases the deviation of CBPs from culturally expected norms but does not eliminate temperament differences. Also, temperament researchers point to the benefits of screening for temperament traits susceptible to the influences the factors of physical environments (exposure to sunlight, infections, toxins, novelty, and variability) [72,74,75]. COVID-19 symptoms are the example of the negative impact of this infection on physical endurance (as fatigue), mental endurance ('covid fog' and inability to focus) and emotional sensitivity (increased symptoms of anxiety) [72].

Overall, a proper differentiation between concepts helps to define variables used in tracing the interactions between parameters of psychophysiology (depicted in an

abstract way as Y-axis, Figure 2) and types of environments (X-axis, Figure 2). The diversity of opinions illustrates a need for conceptual clarity, not only for healthy but also for psychiatric CBPs. Phenotypes defined by the current psychiatric classification systems are also highly heterogeneous, and co-morbidity is highly prevalent [3–5,21]. The ‘simple’ matter of picking and labeling a CBP appears to be neither straightforward nor harmless. The way CBPs are partitioned (divided) into concepts and categories affects not only theories but also their operationalization in assessment tools or as variables in experiments and mathematical modeling [2–6,9,10,19, 21]. Several directions for ‘what's next’ for language biases and conceptual parsing are identified in Table 2.

Mathematics and psychometrics are the tools but not the leading advisers for taxonomic principles and biomarkers

There is a common belief among many practitioners and researchers, that measurement tools in psychology and psychiatry are well tuned, universally applicable and measure what they claim to measure, just like tools in engineering, physics or chemistry. Meanwhile, there are multiple complaints about the low reproducibility and reliability of measurements in behavioral sciences [3–5,9,10].

The complexity and variability of the phenomena that our tools are meant to measure certainly contribute to the challenge of reproducibility; however, there are several ways to handle this problem (Table 2). Much criticism in the biobehavioural sciences is directed to self-reports (questionnaires) and their dependence on their author's theories and arbitrary choices of items. The fundamental problem here, however, is not the self-reporting aspect of questionnaires but rather the lack of a scientific foundation of their association with biological entities [3,10, IT]. After all, self-report is commonly used to access individual experience in many experimental methods (e.g. measurement of perception thresholds and assessment of emotional states), or documentation of psychiatric symptoms.

Main problem of assessment methods (including self-reports) is that they are the end product of the author's understanding (theories), and so ambiguities or deficiencies in these theories can compromise the resulting measurement tools. There are very few psychometric tests that have been validated with behavioral and psychophysiological markers (mostly methods for intelligence and neuropsychological assessments). Practically none of the self-report scales (with the exception of the Structure of Temperament Questionnaire (STQ), derived from neurophysiological studies [15]) were validated this way. Instead, psychometricians are more concerned with ‘evidence’ from confirmatory factor

analysis criteria to pass a test, no matter how dubious the test items might be. To improve the quality of psychological assessment, it might be wise to shift the weight of requirements more to content validity of the scales (verifying it by complementary behavioral measures) and to differential validity (confirming the absence of correlations with unrelated aspects of behavior).

Meanwhile, the historic preference for independence (orthogonality) of scales (whether in self-reports or testing batteries, as in intelligence testing) and the inherent difficulty of determining dimensionality limits the applicability of psychometrically derived taxonomies [10,18]. It is well known that CBP biomarkers, whether brain structures or neurochemical systems, have multiple feedback loops that are contingent on each other's status and possess specific functionality, and, therefore, are partially interdependent.

Linearity in most statistical and psychometric methods is another problem. Regardless of whether a ‘nonlinear’ or ‘Hierarchical’ model is offered in factor-analytic (FA) studies, the analyses are based on matrices of linear correlations, whereas almost all psychological processes show nonlinearity in their associations [10,18,19,85]. Psychometrics provides instruments for our measurements, but cannot substitute analytic work required for hypothesis building. All of this suggests that too much trust in the past was given to psychometrics for proving or disproving proposed associations, whilst there has been too little education on the boundaries of psychometrics [3,10,18].

The consequences of employing simplistic or heterogeneous variables and of the limitations in our theories show up even when we move away from self-reports to using biomarkers. Neuroimaging reports also have low test–retest reliability [4,5,9,17,33], and if variables relate to heterogeneous, poorly defined variables (such as E or PTSD), this can contribute to poor replicability, especially in using fMRI [4,17]. Due to overlaps between responsiveness of the brain regions to different CBPs, they provide little information about the underlying neural processes even though structural MRI can assist in causal explanations of CBPs when it is coupled with well-defined neurological variables. There is ongoing work of cataloging 1:1 associations between biomarkers and CBPs [51]; however, a simple collection of such associations would lead to the modest outcomes similar to the outcomes of the human genome project. It will provide massive information that triggers more questions than answers; that cannot be a desirable end point. We should work more on the evolutionary, systemic and functional principles helping us to classify the numerous CBP–biomarker associations.

More attention should be paid to the fact that biomarkers and CBPs could be classified at several levels of

analysis (genes, their transcription factors and enzymes, hormonal and other neuroendocrine regulation, brain neurotransmitters and their receptors, temperament traits, more culturally-affected aspects of CBPs). Jumping over the levels of biobehavioural regulation (e.g. measuring genes as possible correlates of culturally affected components of personality and not temperament traits) might be a cause of the low replicability of results. As Brandt and Mueller noted, there might be a double-gap problem: one between the observed biological variable and the theoretical psychological process and one between the theoretical psychological process and the observed trait variable. In gene-personality investigations, associations between phenomena are probably mediated by too many intermediate psychophysiological and cultural factors. In contrast to personality traits, temperament traits — such as N, plasticity, endurance or impulsivity, have more potential for consistent associations with biomarkers [1,2,7,9,17,23,35–38,41,53,61,73,81] (Online Etymology Dictionary, <https://www.etymonline.com/word/personality>, retrieved December 2021). When conducting genetic studies of CBPs, therefore, it may be more straightforward to use more neurochemically based CBPs, such as temperament traits or symptoms of psychiatric disorders. Also, there should be more discussions about the formal analysis of gene–environment interaction [21,33,50] (Online Etymology Dictionary, <https://www.etymonline.com/word/personality>, retrieved December 2021).

Mathematical, statistical and machine learning methods, while useful, are limited in capacity to represent complex transient phenomena, such as CBPs [1,10,17], and are only as good as the measurement tools. Merely performing calculations with arbitrary variables will not be fruitful. Thus, work is needed to ‘clean up’ the content of variables and hypotheses. Alternative multivariate mathematical approaches, such as nonlinear methods, time series, Bayesian, and stochastic models, are currently being explored. These methods might help in dealing with context dependence and variability of CBPs [5,10,54,86,87]. Ensemble-like models such as process algebra (cited in Refs. [10,19,54]) and functional constructivism [2,24] have been proposed for the systematic analysis of functional relationships between biomarkers and individual–environment interaction [2,5,36]. However, these are all works in progress because current number systems can process only repetitive occurrences with defined parameters but not one-time occurrences, in which features emerge and disappear [1,2,10].

There is also a disconnect between training in neuroscience and psychology, which leads to misconceptions in neuroscience as to how psychological phenomena form CBP (mostly in behaviorist language) and misconceptions in psychology as to how the nervous system operates [1].

International cooperation and perspective methods

Research during the past century revealed the complexity and diversity of CBP, their contextuality, clinical, ontogenetic, interspecies continua, as well as variance coming from biochemical environmental factors (climates, diets, exposure to toxins, and psychostimulants). Moreover, as noted above, biomarkers of CBP appear to involve not only the brain, but also neuro-immune, enteric, and endocrine systems. Multidisciplinary study of these systems and their dynamics is needed to arrive at a proper classification of CBP for healthy biobehavioral traits and symptoms of psychopathology.

International cooperation and a structured approach to ‘big data’ is, therefore, the next necessary step in this line of research. It is essential that future international projects consider approaches, methods and aspects of such cooperation listed in [Tables 1 and 2](#).

Conclusions

To summarize, as a perspective on ‘what's next’ in the development of CBP taxonomies, there is a consensus that this work cannot progress if psychology and psychiatry continue looping around the poorly defined and overlapping concepts within these sciences. Instead, multidisciplinary cooperation and adaptation of knowledge from other sciences is needed in the form of joint discussions, advanced study schools for specialists, forums, research, publications, and online platforms. The need for a science of biomarkers underlying behavioral regulation and specific CBPs exists not just in terms of brain neuroimaging studies, but also in relation to other systems, such as endocrine, enteric and immune systems, and their interactions with brain neurochemistry. In addition to experimental research, analytic discussions should be expanded to generate testable theories and identify principles underlying these interactions, along with new methods for their analysis.

Several such principles have been identified, but have not yet been properly incorporated into the structure of psychiatric and psychological classifications: a continuum between health and psychopathology; an ontogenetic continuum; the importance of the context-dependence and intra-individual variability of behavior; species-ecological continua explored through research using animals; sex/gender related variables; the constructive nature of behavior; the contributions of regional environmental biochemical factors (e.g. amount of sunlight, diets, and use of psychostimulants). A few of these principles are illustrated in [Figures 1 and 2](#).

The history of physics, chemistry, biology, and medicine demonstrates that it takes time to derive adequate taxonomies and their appropriate organizing principles.

The multiplicity and complexity of the systems contributing to the consistency of behavioral patterns, the high transience and complexity of CBP that differential psychology and psychiatry attempt to classify, suggest that there is still a long road ahead. The good news from this paper, then, is that we have reached a point where we can agree on our disagreements and so have taken the first step to solving them. More importantly, this capacity to disagree rests on a substantial consensus and much common language that should provide a solid foundation for future work.

Conflict of interest statement

All other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

This article provides a debate and discussion of the issues in the field, prepared in collaboration by the authors from this special issue. As an editorial/commentary rather than a formal review, it did not undergo formal external review, although all authors participated in and provided comments on the full article. Final editorial evaluation was delegated to Cindy Lustig (Editor-in-Chief). As authors on the paper, the Guest Editors and Trevor Robbins (Editor-in-Chief) had no involvement in the editorial evaluation of this piece.

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