PHILOSOPHICAL TRANSACTIONS B

rstb.royalsocietypublishing.org

Review

**Cite this article:** Cloninger CR, Zwir I. 2018 What is the natural measurement unit of temperament: single traits or profiles? *Phil. Trans. R. Soc. B* **373**: 20170163.
http://dx.doi.org/10.1098/rstb.2017.0163

Accepted: 24 November 2017

One contribution of 20 to a theme issue 'Diverse perspectives on diversity: multi-disciplinary approaches to taxonomies of individual differences'.

**Subject Areas:**
genomics, behaviour

**Keywords:**
temperament, complex adaptive systems, genetic pleiotropy, epistasis, unsupervised machine learning

**Author for correspondence:**
C. Robert Cloninger
e-mail: c.robert.cloninger@wustl.edu

# What is the natural measurement unit of temperament: single traits or profiles?

C. Robert Cloninger and Igor Zwir

Department of Psychiatry, Washington University Medical School, 660 S. Euclid, St Louis, Missouri 63110, USA

CRC, 0000-0003-3096-4807; IZ, 0000-0002-1443-0234

There is fundamental doubt about whether the natural unit of measurement for temperament and personality corresponds to single traits or to multi-trait profiles that describe the functioning of a whole person. Biogenetic researchers of temperament usually assume they need to focus on individual traits that differ *between* individuals. Recent research indicates that a shift of emphasis to understand processes *within* the individual is crucial for identifying the natural building blocks of temperament. Evolution and development operate on adaptation of whole organisms or persons, not on individual traits or categories. Adaptive functioning generally depends on feedback among many variable processes in ways that are characteristic of complex adaptive systems, not machines with separate parts. Advanced methods of unsupervised machine learning can now be applied to genome-wide association studies and brain imaging in order to uncover the genotypic–phenotypic architecture of traits like temperament, which are strongly influenced by complex interactions, such as genetic epistasis, pleiotropy and gene–environment interactions. We have found that the heritability of temperament can be nearly fully explained by a large number of genetic variants that are unique for multi-trait profiles, not single traits. The implications of this finding for research design and precision medicine are discussed.

This article is part of the theme issue 'Diverse perspectives on diversity: multi-disciplinary approaches to taxonomies of individual differences'.

## 1. Introduction

### (a) What are the natural building blocks of temperament?

Despite the long history of studying individual differences in temperament traits, there remains fundamental uncertainty about the definition of temperament, including what to measure and how to measure it. Generally, temperament refers to those aspects of personality that are biologically based rather than learned. However, even this basic definition is problematic because human beings have three major systems of learning and memory that each has a distinct genetic and biological basis: associative conditioning of habits and skills, declarative learning of facts, and autonoetic learning of a personal lifetime narrative [1–3]. Early temperament research emphasized the assessment of features of activity and affectivity that were developmentally stable, but more recent work has suggested that temperament may include attention and self-regulatory processes [4], which emerged later in evolution [5] and develop into adulthood in response to individual experience and social norms [6].

There is also fundamental doubt about whether the natural biological unit of measurement for temperament and other personality traits corresponds to individual traits or multi-trait configurations. Researchers of temperament and its biology usually focus on individual traits that differ between individuals [4]. By contrast, developmental and social-cognitive psychologists usually focus on multi-trait configurations within each individual because these are more stable developmentally and more informative about internal psychobiological processes [7–9].

THE ROYAL SOCIETY PUBLISHING

### (b) Multi-disciplinary evidence of complexity in development

There is widespread agreement that temperament is the product of complex interactions among genetic, biological and environmental influences across time in adaptation to ever-changing conditions and experiences [4,9–12]. Brain circuitry related to human temperament shows extensive feedback interactions that are characteristic of complex adaptive systems [11,13,14]. Longitudinal studies show strong evidence of developmental complexity: individuals with the same antecedent traits may have different outcomes (i.e. multifinality) and those with different antecedent traits may have the same outcome (i.e. equifinality) [15–17].

In general, evolution and development operate on the adaptation of whole organisms or persons, not on individual traits or categories [5,14]. Adaptive functioning generally depends on feedback among many variable processes in ways that are characteristic of non-linear dynamical systems, not machines with separate parts [16].

The heritability of temperament traits is estimated to be 30–60% based on twin studies [17–20]. However, studies of twins along with other family members show that most of the heritability of temperament is likely to depend on complex interactions among multiple gene loci (i.e. epistasis) and environmental influences (i.e. gene–environment interaction) [21–23]. Consequently, it is no surprise that genome-wide association studies (GWASs) that consider only the average effects of genes have explained little of the heritability of temperament [12,24,25].

The failure to identify specific genes to account for the heritability of complex traits has been called the 'missing' [26] or 'hidden' [27] heritability problem. Fortunately, advanced methods of deep unsupervised machine learning have been developed for uncovering the hidden architecture of complex traits like temperament in ways that are unencumbered by restrictive hypotheses like additive gene action [17,28,29]. These methods provide a data-driven way to describe the complex genotypic–phenotypic relationships needed to develop an adequate taxonomy and psychobiology of temperament. Such data-driven methods are useful to complement theory-driven approaches to these questions [30,31].

## 2. Methodological recommendations: utility of deep unsupervised learning methods

Unsupervised machine learning provides a strictly data-driven method for uncovering complex latent architectures, such as patterns of connectivity in functional brain imaging and/or genotypic–phenotypic relationships in GWASs [17,28,29,32]. This person-centred approach focuses on identifying patterns of relationship within individuals, rather than on average differences between groups of people with heterogeneous features. Cluster analysis based on non-negative matrix factorization (NMF) can be used to optimize pattern recognition and identification of naturally occurring associations of patterns across different types of data. Our generalized clustering method, which is an extension of typical clustering methods, allows observations on subjects who may appear in multiple clusters in association with different features [17,28,29]. Our clustering approach is entirely data-driven without restrictive assumptions about the number or content of the clusters. Such clustering is a hypothesis-generating method in which there is no unique solution to the number of clusters, what features are relevant for a cluster, or the degree of homogeneity required for a cluster. Practical solutions are applied to manage each of these issues in our Web server application PGMRA, which is published and accessible online [28]. Expert peer-review has consistently recognized the value and validity of our use of generalized clustering methods in bioinformatics [28], genetics [17] and brain imaging [29]. Replication in independent samples provides an empirical test of the robustness of the results.

The generalized clustering method implemented in PGMRA can be interpreted as a deep unsupervised NMF learning process to identify clusters of individuals with distinct features in various domains of knowledge, such as genotypes, phenotypes and environments. Such clusters may be used as auto-encoders or recommender systems in precision medicine. The utility of this approach is that the complex architecture of relationships between the measured domains is uncovered so that investigators are not forced to rely upon unrealistic assumptions like additive gene action, and can specify the 'many to many' relationships between phenotypic domains and other variables, such as brain connectivity, genotypes and/or environments.

## 3. Illustrative results

### (a) Complex architecture of the schizophrenias and schizotypy

Using PGMRA we found that schizophrenia is a group of heritable disorders caused by a moderate number of separate genotypic networks associated with distinct clinical syndromes [17]. In a large GWAS of cases with schizophrenia and controls, the authors first identified sets of interacting single-nucleotide polymorphisms (SNPs) that cluster within particular individuals (SNP sets) regardless of clinical status. Second, they examined the risk of schizophrenia for each SNP set and tested replicability in two independent samples. Third, they identified genotypic networks composed of SNP sets sharing SNPs or subjects. Fourth, they identified sets of distinct clinical features that cluster in particular cases (phenotypic sets or clinical syndromes) without regard for their genetic background. Fifth, they tested whether SNP sets were associated with distinct phenotypic sets in a replicable manner across the three studies.

Forty-two SNP sets associated with a 70% or greater risk of schizophrenia were identified, and 34 (81%) were confirmed and found to have a similar high risk of schizophrenia in two independent samples. The interactive networks explained the risk of schizophrenia much more precisely (70–100%) than the average effects of all SNPs (24%). As a result, allowing for epistasis permitted the authors to predict schizophrenia with high precision, thereby laying the foundation for effective intervention in individual cases.

Seventeen networks of SNP sets were disjoint (that is, they did not share any SNP or subject), suggesting heterogeneous gene sets can predispose a person to a form of schizophrenia. These disjoint genotypic networks were associated with distinct gene products and clinical syndromes (i.e. the schizophrenias) varying in symptoms and severity. Associations between genotypic networks and clinical

syndromes were complex, showing multifinality and equifinality. Consequently, description of the genotypic–phenotypic pathways requires joint consideration of both genotypes and phenotypes at the same time, rather than trying to define the pathway in either a top-down (clinical features to causes, as in strictly clinical classifications) or a bottom-up (causes to outcomes, as in reductive molecular approaches) perspective.

These GWAS findings showed that it is possible to distinguish subtypes of schizophrenias with distinct genetic and clinical features with high precision, sufficiently to inform the assessment and treatment of individuals. In order to further test the power of the deep NMF learning approach, the authors investigated whether the identified subtypes of schizophrenia could be distinguished by distinct patterns of white matter anisotropy in diffusion tensor imaging of 47 patients with schizophrenia and 36 healthy controls. Despite the small size of the sample, four patterns of fractional anisotropy were distinguished and found to be associated with distinct clinical subtypes like those in the GWAS.

Tests of overlap between the genes for schizophrenia and those for schizotypal personality traits identified in other work found minimal overlap, but further work is needed in studies of schizotypy and schizophrenia in the same sample because there may be heterogeneous pathways to schizotypy, just as there are for the schizophrenias.

### (b) Building blocks of temperament are multi-trait profiles, not single traits

The same deep NMF learning methods have also been applied to a GWAS of personality assessed by the temperament and character inventory (TCI) in three large independent samples from Finland [33], Germany [34] and South Korea [35]. The TCI measures four dimensions of temperament (Novelty Seeking, Harm Avoidance, Reward Dependence and Persistence) and three dimensions of character (Self-directedness, Cooperativeness and Self-transcendence) [10]. All of these dimensions have strong test–retest reliability and are about 40–55% heritable according to twin studies [18,36].

However, TCI temperament traits show strong evidence of non-additive gene action, and prior GWASs assuming that gene action was additive had failed to explain much of the expected heritability [23,25]. By contrast, by allowing for epistasis in our person-centred GWAS, we uncovered SNP sets that explained nearly all of the expected heritability (37 to 53%) in three independent samples. The SNP sets had complex relations with phenotypic sets based on the TCI traits, including multifinality (i.e. genetic pleiotropy) and equifinality (genetic heterogeneity).

Most surprisingly, when the SNP sets were grouped according to the temperament profiles with which they were associated, we found that approximately 69% of the genes mapped to these SNPs were unique to a single temperament profile. The genes associated with different temperament profiles were mostly unique to that profile and influenced distinct molecular processes and neuronal functions.

## 4. Discussion

The development of cluster analytic methods utilizing deep unsupervised machine learning provides an excellent opportunity to uncover the complex genotypic–phenotypic architecture of human temperament in an unbiased data-driven manner without restrictive assumptions. In the past, psychologists, biologists and geneticists have usually assumed that single traits are the natural building blocks of temperament and that these become integrated in multi-trait profiles during development. However, our data-driven analytical methods show that genes largely code for multi-trait profiles that describe the whole person, not individual traits.

For example, a person who scores high in the three temperaments of Novelty Seeking (i.e. impulsive), Harm Avoidance (i.e. pessimistic, anxious) and Reward Dependence (i.e. warmly sociable) is described as 'sensitive' because of the many emotional conflicts that usually arise with this set of traits. Another person who is high in Reward Dependence is described as 'reliable' if they are also low in Novelty Seeking (i.e. deliberate) and Harm Avoidance (i.e. optimistic), rather than being high in these traits. If the genes for the sensitive and reliable profiles are different, then there will be genetic heterogeneity in people with Reward Dependence. Put another way, individuals who share features of a single trait do so as the result of different mechanisms, which can be distinguished by consideration of other traits that are presented by that person. Therefore, it is important to consider the configuration of multiple traits that describe each person as a whole in order to be able to distinguish the different molecular and biological processes that influence temperament. We recommend that multi-trait profiles be used routinely to measure temperament rather than individual traits.

This recommendation has many implications for assessment and research of temperament. First, it means that greater attention to the configuration of features present within a person is crucial in order to understand the genetic and biological basis of temperament, rather than focusing on differences in single traits between individuals. Second, it indicates that joint consideration of genetic and phenotypic information is important for precise specification of the genotypic–phenotypic pathway. Third, a developmental perspective is important for understanding the complex 'many to many' relationship between genotypes and phenotypes.

The importance of focusing on the configuration of traits that describe the whole person does not mean that recognition of individual traits is no longer useful. It only means that single traits cannot be assumed to be the natural building blocks of temperament. Individual traits may still be of interest for understanding the way they emerge from the integration of different mechanisms associated with distinct multi-trait profiles in response to adaptive challenges during development. However, without joint information about genotypic predisposition and comprehensive phenotypic information, it is impossible to predict with precision how a person will respond to behavioural conditioning and other forms of learning and/or treatment of any kind, including psychopharmacology.

The complexity that we have already recognized confirms the need for transdisciplinary work that takes into account the contributions of many disciplines, as described by others [30,37] elsewhere and in this special issue.

Data accessibility. This article has no additional data.

Competing interests. We have no competing interests.

Funding. This work was supported in part by the Center for Psychobiology of Personality at Washington University in St Louis, NIH grant R01MH060879 to C.R.C., and the Spanish Ministry of Science and Technology grants TIN2012-38805 and DPI2015-69585-R to I.G.

## References


1. Tulving E. 2001 Episodic memory and common sense: how far apart? *Phil. Trans. R. Soc. Lond. B* **356**, 1505–1515. (doi:10.1098/rstb.2001.0937)
2. Tulving E. 1987 Multiple memory systems and consciousness. *Hum. Neurobiol.* **6**, 67–80.
3. Cloninger CR, Abou-Saleh MT, Mrazek DA, Möller H-J. 2011 Biological perspective on psychiatry for the person. *Int. J. Pers. Cent. Med.* **1**, 137–139. (doi:10.5750/ljpcm.v1i1.35)
4. Shiner RL, Buss KA, McClowry SG, Putnam SP, Saudino KJ, Zentner M. 2012 What is temperament now? Assessing progress in temperament research on the twenty-fifth anniversary of Goldsmith *et al*. (1987). *Child Dev. Perspect.* **6**, 436–444. (doi:10.1111/j.1750-8606.2012.00254.x)
5. Cloninger CR. 2009 The evolution of human brain functions: the functional structure of human consciousness. *Aust. N. Z. J. Psychiatry* **43**, 994–1006. (doi:10.1080/00048670903270506)
6. Josefsson K, Jokela M, Cloninger CR, Hintsanen M, Salo J, Hintsa T, Pulkki-Råback L, Keltikangas-Järvinen L. 2013 Maturity and change in personality: developmental trends of temperament and character in adulthood. *Dev. Psychopathol.* **25**, 713–727. (doi:10.1017/S0954579413000126)
7. Cloninger CR. 2003 Completing the psychobiological architecture of human personality development: temperament, character, and coherence. In *Understanding human development: dialogues with lifespan psychology* (eds UM Staudinger, UER Lindenberger), pp. 159–182. London, UK: Kluwer Academic Publishers.
8. Cervone D. 2005 Personality architecture: within-person structures and processes. *Annu. Rev. Psychol.* **56**, 423–452. (doi:10.1146/annurev.psych.56.091103.070133)
9. Staudinger UM, Lindenberger U (eds). 2003 *Understanding human development: dialogues with lifespan psychology*. London, UK: Kluwer Academic Publishers.
10. Cloninger CR, Svrakic DM, Przybeck TR. 1993 A psychobiological model of temperament and character. *Arch. Gen. Psychiatry* **50**, 975–990. (doi:10.1001/archpsyc.1993.01820240059008)
11. Van Schuerbeek P, Baeken C, De Raedt R, De Mey J, Luypaert R. 2011 Individual differences in local gray and white matter volumes reflect differences in temperament and character: a voxel-based morphometry study in healthy young females. *Brain Res.* **1371**, 32–42. (doi:10.1016/j.brainres.2010.11.073)
12. de Moor MH *et al*. 2012 Meta-analysis of genome-wide association studies for personality. *Mol. Psychiatry* **17**, 337–349. (doi:10.1038/mp.2010.128)
13. Van Schuerbeek P, Baeken C, Luypaert R, De Raedt R, De Mey J. 2014 Does the amygdala response correlate with the personality trait 'harm avoidance' while evaluating emotional stimuli explicitly? *Behav. Brain Funct.* **10**, 18. (doi:10.1186/1744-9081-10-18)
14. Cloninger CR, Kedia S. 2011 The phylogenesis of human personality: identifying the precursors of cooperation, altruism, and well-being. In *The origins of cooperation and altruism*, 1st edn (eds RW Sussman, CR Cloninger), pp. 63–110. New York, NY: Springer.
15. Cicchetti D, Rogosch FA. 1996 Equifinality and multifinality in developmental psychopathology. *Dev. Psychopathol.* **8**, 597–600. (doi:10.1017/S0954579400007318)
16. Cloninger CR, Svrakic NM, Svrakic DM. 1997 Role of personality self-organization in development of mental order and disorder. *Dev. Psychopathol.* **9**, 881–906. (doi:10.1017/S095457949700148X)
17. Arnedo J *et al*. 2015 Uncovering the hidden risk architecture of the schizophrenias: confirmation in three independent genome-wide association studies. *Am. J. Psychiatry* **172**, 139–153. (doi:10.1176/appi.ajp.2014.14040435)
18. Gillespie NA, Cloninger CR, Heath AC, Martin NG. 2003 The genetic and environmental relationship between Cloninger's dimensions of temperament and character. *Pers. Individ. Differ.* **35**, 1931–1946. (doi:10.1016/S0191-8869(03)00042-4)
19. Tellegen A, Lykken TD, Bouchard TJ, Wilcox KJ, Segal NL, Rich S. 1988 Personality similarity in twins reared apart and together. *J. Pers. Soc. Psychol.* **54**, 1031–1039. (doi:10.1037/0022-3514.54.6.1031)
20. Yamagata S *et al*. 2006 Is the genetic structure of human personality universal? A cross-cultural twin study from North America, Europe, and Asia. *J. Pers. Soc. Psychol.* **90**, 987–998. (doi:10.1037/0022-3514.90.6.987)
21. Keller MC, Coventry WL, Heath AC, Martin NG. 2005 Widespread evidence for non-additive genetic variation in Cloninger's and Eysenck's personality dimensions using a twin plus sibling design. *Behav. Genet.* **35**, 707–721. (doi:10.1007/s10519-005-6041-7)
22. Verweij KJ *et al*. 2012 Maintenance of genetic variation in human personality: testing evolutionary models by estimating heritability due to common causal variants and investigating the effect of distant inbreeding. *Evolution* **66**, 3238–3251. (doi:10.1111/j.1558-5646.2012.01679.x)
23. Verweij KJH *et al*. 2010 A genome-wide association study of Cloninger's temperament scales: implications for the evolutionary genetics of personality. *Biol. Psychol.* **85**, 306–317. (doi:10.1016/j.biopsycho.2010.07.018)
24. Munafo MR, Flint J. 2011 Dissecting the genetic architecture of human personality. *Trends Cogn. Sci.* **15**, 395–400. (doi:10.1016/j.tics.2011.07.007)
25. Service SK *et al*. 2012 A genome-wide meta-analysis of association studies of Cloninger's temperament scales. *Transl. Psychiatry* **2**, e116. (doi:10.1038/tp.2012.37)
26. Eichler EE, Flint J, Gibson G, Kong A, Leal SM, Moore JH, Nadeau JH. 2010 Missing heritability and strategies for finding the underlying causes of complex disease. *Nat. Rev. Genet.* **11**, 446–450. (doi:10.1038/nrg2809)
27. Williams SM, Haines JL. 2011 Correcting away the hidden heritability. *Ann. Hum. Genet.* **75**, 348–350. (doi:10.1111/j.1469-1809.2011.00640.x)
28. Arnedo J, del Val C, de Erausquin GA, Romero-Zaliz R, Svrakic D, Cloninger CR, Zwir I. 2013 PGMRA: a web server for (phenotype × genotype) many-to-many relation analysis in GWAS. *Nucleic Acids Res.* **41**(Web Server issue), W142–W149. (doi:10.1093/nar/gkt496)
29. Arnedo J, Mamah D, Baranger DA, Harms MP, Barch DM, Svrakic DM, De Erausquin GA, Cloninger CR, Zwir I. 2015 Decomposition of brain diffusion imaging data uncovers latent schizophrenias with distinct patterns of white matter anisotropy. *Neuroimage* **120**, 43–54. (doi:10.1016/j.neuroimage.2015.06.083)
30. Uher J. 2013 Personality psychology: lexical approaches, assessment methods, and trait concepts reveal only half of the story—why it is time for a paradigm shift. *Integr. Psychol. Behav. Sci.* **47**, 1–55. (doi:10.1007/s12124-013-9230-6)
31. Uher J. 2015 Interpreting 'personality' taxonomies: why previous models cannot capture individual-specific experiencing, behaviour, functioning and development. Major taxonomic tasks still lay ahead. *Integr. Psychol. Behav. Sci.* **49**, 600–655. (doi:10.1007/s12124-014-9281-3)
32. Hinton GE, Salakhutdinov RR. 2006 Reducing the dimensionality of data with neural networks. *Science* **313**, 504–507. (doi:10.1126/science.1127647)
33. Raitakari OT *et al*. 2008 Cohort profile: the Cardiovascular Risk in Young Finns Study. *Int. J. Epidemiol.* **37**, 1220–1226. (doi:10.1093/ije/dym225)
34. Cook TB *et al*. 2015 Latent infection with *Toxoplasma gondii*: association with trait aggression and impulsivity in healthy adults. *J. Psychiatr. Res.* **60**, 87–94. (doi:10.1016/j.jpsychires.2014.09.019)
35. Sung J *et al*. 2006 Healthy twin: a twin-family study of Korea—protocols and current status. *Twin Res. Hum. Genet.* **9**, 844–848. (doi:10.1375/183242706779462822)
36. Heath AC, Cloninger CR, Martin NG. 1994 Testing a model for the genetic structure of personality: a comparison of the personality systems of Cloninger and Eysenck. *J. Pers. Soc. Psychol.* **66**, 762–775. (doi:10.1037/0022-3514.66.4.762)
37. Trofimova I, Robbins TW. 2016 Temperament and arousal systems: a new synthesis of differential psychology and functional neurochemistry. *Neurosci. Biobehav. Rev.* **64**, 382–402. (doi:10.1016/j.neubiorev.2016.03.008)