The link between mitochondria, psychopathology, and intelligence: A bioenergetic model of cerebral function

Dr. Patrick Fissler^{1,2*}, M.Sc. R. Nehir Mavioglu³, M.Sc. Maya Wenzel^{1,2,4}, M.Sc. Marco Filippi^{1,2,4}, Dr. Steffen Stoewer^{1,2,5}, PD Wanja Wolff^{6,7}, Dr. Alexander Karabatsiak⁸, Prof. Jens C. Pruessner⁴, Prof. Iris-Tatjana Kolassa³, PD Rainer Krähenmann^{1,2,9}

¹ Psychiatric Services Thurgau, Seeblickstrasse 3, 8596 Münsterlingen, Switzerland

² University Hospital for Psychiatry, Psychotherapy and Psychosomatics, Paracelsus Medical University, Strubergasse 21, 5020 Salzburg, Austria

³ Clinical and Biological Psychology, Ulm University, Albert-Einstein-Allee 47, 89081 Ulm, Germany

⁴ Neuropsychology, University of Konstanz, Postfach 905, 78457 Konstanz, Germany

⁵ Psychiatric Services Aargau, Windisch, Switzerland

⁶ Department of Sport Science, University of Konstanz, Postfach 30, 78457 Konstanz, Germany

⁷ Department of Educational Psychology, University of Bern, Hochschulstrasse 6, 3012 Bern, Switzerland

⁸ Department of Clinical Psychology, University of Innsbruck, Innrain 52f, 6020 Innsbruck, Austria

⁹ Department of Psychiatry, Psychotherapy and Psychosomatics, University of Zürich, Lenggstrasse 31, 8032 Zürich, Switzerland

* Correspondence: Dr. Patrick Fissler, Psychiatric Services Thurgau, Seeblickstrasse 3, 8596 Münsterlingen, Switzerland, email: patrick.fissler@stgag.ch, telephone: +41 71 686 4347

Author Contribution

PF conceptualized the bioenergetic model of cerebral function with critical contributions from ITK, AK and RK. PF, RK, RNM & SS wrote the first draft of the manuscript. All authors searched the literature and contributed to the ideas developed in the paper, edited and revised the manuscript in a critical and important manner. PF created the figures.

Acknowledgements

We thank Prof. Dr. med. Christine von Arnim and Dipl.-Psych. Anne Plischke for exchanging their ideas, knowledge, views, and experiences that critically and importantly contributed to this manuscript. We had no external funding for this work.

Conflict of Interest

All authors report no conflicting interests.

Abstract

Decomposing the structure of human cerebral function in its constituent domains forms the backbone of diagnosis and treatment of psychological and neurocognitive disorders. Research continues to decipher the domains and hierarchical structure of cerebral function. So far, the findings strongly suggest two higher-order latent factors of general *psychopathology* (*p* factor) and general intelligence (*g* factor). Both general factors are functions of the same organ. They covary, share risk factors as well as biomarkers, and benefit from the same treatments. However, to our knowledge, a model that connects both components of cerebral function within a higher-order latent factor and describes its potential biological underpinning is lacking. Here, we address this gap. First, we suggest the general factor of cerebral function (*c* factor) as the shared variance of the measures of *g* and *p* in a bi-factor model. Second, we review evidence that mitochondrial bioenergetics (MB) is one core biological underpinning of *c*. Third, we describe how this *c* factor mito-bioenergetics (CMB) model may transform research and clinical practice by advancing knowledge of treatment effects, risk factors, biomarkers, and clinical outcomes.

1. Introduction

A large body of literature has consistently shown that performance across different cognitive tasks covaries.¹ Along the same lines, numerous studies demonstrate a covariation among different psychological symptoms.² Hierarchical models of intelligence and psychopathology that map these covariations on the latent factors of general intelligence and general psychopathology have been developed.^{1,3,4} These general factors were termed *g* and *p*, respectively.^{1,3} The models of *g* and *p*—such as the Hierarchical Taxonomy of Psychopathology (HiTOP) model—are data-driven and still progressing.^{3,5-7} Here, we review several lines of research indicating a common factor that connects *g* and *p*. To our knowledge, no theoretical or empirical model conceptualizes this higher-order latent factor that we call the general factor of cerebral function—the *c* factor.

Recent models outline the role of mitochondrial bioenergetics (MB)—the mitochondrial energy production mechanisms—in *g* and *p*.⁸⁻¹¹ However, these are separate models that do not provide an umbrella conceptualization of the general cerebral function that subsumes the shared variance of the measures of *g* and *p*. Therefore, MB may be mistakenly attributed as a specific biological mechanism of *g* and *p*, while it may truly load on the *c* factor, the highest level in the taxonomy of cerebral function.

In this review paper, we introduce the *c* factor mito-bioenergetics (CMB) model. We propose that MB is one core mechanism responsible for the shared variance between the measures of *g* and *p* (*c* factor; see Figure 1). First, we review evidence on the validity of the *g* and *p* factor. Second, we introduce the *c* factor by reviewing the shared variance and co-occurrence of the *g* and *p* factor symptoms in both symptomatically defined psychiatric disorders (e.g., depression, schizophrenia spectrum disorder, and dementia) as well as in biologically defined diseases of the brain (e.g., Alzheimer's disease, phenylketonuria, and multiple sclerosis). Third, we describe the basics of MB and review the evidence on MB as a biological correlate of general cerebral function. Fourth, we outline the research and clinical implications of the CMB model within a transdiagnostic framework, a promising approach still in its infancy.¹²

2. The *g* and *p* factor

General factor models of different cerebral functions have become widely accepted.⁷ These models range from general factors of fluid intelligence, emotional intelligence, psychopathology, personality, and personality disorder to a general factor of personality organization.^{1,3,4,13-16} While general factor models have not been fully undisputed, their validity

results from two long-known observations: (i) high associations between different cognitive abilities (g factor) and (ii) high comorbidity between different psychological disorders, which is reflected in high correlations between the extent of different psychological symptoms (p factor). In other words, people who perform well in one cognitive task typically perform well in other cognitive tasks too. People with one psychological disorder or with one symptom often have another disorder or another symptom at the same time (simultaneous comorbidity) or tend to develop another disorder or symptom in the future (sequential comorbidity). The idea is that general latent factors explain a large part (i) of the performance in different cognitive tasks (g factor) and (ii) of different psychological symptoms (p factor). These two higher-level concepts have been successfully validated in structural equation models.^{1,3,4} Comparing the validity of p and g in an adult sample revealed very similar positive results for both general factors.¹⁷ Based on psychiatric diagnoses, the variance accounted for by p was 0.48.¹⁷ The variance in intelligence subtests that was accounted for by g was 0.49.¹⁷ This means that the magnitude of both general factors is of a very similar size.¹⁷ The exact taxonomy of the subdomains of p and g is currently under development and no consensus has been established.^{3,5-7} Well validated hierarchical models include the HiTOP model for the p factor, and the Berlin Intelligence Structure (BIS) model or the Cattell-Horn-Carroll model for the g factor.^{5,6,18}

3. The c factor

To our knowledge, the highest level in the taxonomy of cerebral function—the so-called c factor—that links p and g has not been conceptualized so far. The c factor represents the common variance of measures of its two sub-domains, g and p (see Figure 1). The c factor connects p factor models with g factor models. In all p and g factor models, the symptoms of the p factor and the abilities of the g factor are grouped within multiple levels based on their observable covariation (e.g., p with its subdomains internalizing and externalizing symptoms, g with its subdomains episodic memory and executive function).^{3,19} To reveal treatment effects, risk factors, biological mechanisms, and clinical outcomes for the distinct domains of cerebral function, bi- or tri-factor models should be used (one manifest item loads on two or three latent factors). This structural equation modelling approach enables the extraction of pure measures of each domain, separating variance that is due to broad higher-order domains and more narrow lower-order domains (see Figure 1).²⁰

Figure 1 - The c factor model. The c factor is defined as the shared variance of g and p factor measures. These measures load not only on c but also on g and p (within bi-factor models; one item loads on two latent factors) and their respective sub-factors (Internalizing, Externalizing, Executive Function, Episodic Memory; within tri-factor models; one item loads on three latent factors). By accounting for the shared variance of measures of g and p, the c factor can be extracted and the pure measures of the second- and third-order factors can be revealed. Decomposing of cerebral function is necessary to reveal which treatments have an effect on which order of cerebral function and on which domain. In the same vein, links of biological mechanisms, risk factors, and clinical outcomes with pure measures of each domain on different hierarchical levels can be revealed (see Figure 3). c = c factor or general cerebral function; EF = executive function and attention; EM = episodic memory; Ext = externalizing symptoms; g = g factor or general intelligence; Int = internalizing symptoms; M = manifest variable; p = p factor or general psychopathology

Evidence for the c factor: The link between the p and g factor

Importantly, the measures of g and p covary in cross-sectional and longitudinal studies.^{3,21} Second, psychological and cognitive symptoms co-occur in most symptomatically defined psychiatric disorders including depression, schizophrenia, posttraumatic stress disorder and neurocognitive disorders such as dementia.²²⁻²⁵ This means that cognitive impairment is common in psychological disorders with similar cognitive impairment in internalizing, externalizing and thought disorders.³ Similarly, psychological symptoms are extremely common in neurocognitive disorders. Up to 80% of dementia patients suffer from at least one psychological symptom.²⁵ Third, in biologically defined diseases of the brain, psychological and cognitive symptoms co-occur often. In Alzheimer's disease (defined by high amyloid and tau pathology), multiple sclerosis (fluctuating white matter hyperintensities connected to inflammation), and phenylketonuria (disturbance in phenylalanine metabolism), cognitive impairment was predominantly described, but recent research indicates that psychological symptoms are also common.²⁶⁻³¹ In Alzheimer's disease, even decades before functional

impairment, individuals showed an increased risk for depression.²⁶ Similarly, individuals without dementia but carriers for APOE allele 4, a genetic risk factor for Alzheimer's disease, have an increased risk for depression.²⁷ Most importantly, dominantly inherited Alzheimer's disease patients show personality changes—a measure of p as showed above—many years before the onset of dementia.^{14,28} This means that Alzheimer's disease affects not only measures of g but also of p. It is well known that in other diseases of the brain, such as multiple sclerosis and phenylketonuria, the measures of both the g and p factor are impaired.²⁹⁻³¹

4. The c factor mito-bioenergetics model

In addition to proposing the c factor, we suggest in the CMB model that one core underlying biological mechanism of c is the regulation of MB (see Figure 2). We propose that MB is one of the mechanisms that underlies the covariation between p and g. In other words, MB links p and g. In the following section, we briefly describe the basics of MB and provide evidence for the CMB model.

Figure 2 – The c factor mito-bioenergetics (CMB) model. The model assumes that mitochondrial bioenergetics is one core biological underpinning of the c factor. c = c factor or general cerebral function; EF = executive function and attention; EM = episodic memory; Ext = externalizing symptoms; g = g factor or general intelligence; Int = internalizing symptoms; M = manifest variable; MB = mitochondrial bioenergetics; p = p factor or general psychopathology

Basics of mitochondrial bioenergetics

The brain is the body's largest energy consumer (20%), and neurons spend 75–80% of the energy produced in the brain.³² Energy homeostasis within neurons is of paramount importance for neuronal function. Energy production in the human body can happen in two different ways: aerobic and anaerobic respiration. In anaerobic respiration, glucose is converted to pyruvate by glycolysis, and adenosine triphosphate (ATP) is produced. Then, pyruvate is converted to lactic acid with a process called lactic acid fermentation. The main locus of energy production through aerobic respiration is the mitochondrion, which produces ATP as fuel through a delicate cascade of processes called oxidative phosphorylation (OXPHOS). After glycolysis, pyruvate is metabolized to acetyl-coA to enter into the tricarboxylic acid cycle (TCA). Apart from pyruvate, fatty acids can also be carried inside the mitochondrion with the help of carnitine and can be converted to acetyl-coA via beta-oxidation.³³ Electrons are carried by NADH and FADH₂ generated during glycolysis, TCA and fatty acid oxidation, and used in the electron transport chain (ETC). ETC consists of four different enzymatic complexes, including complex IV, where oxygen acts as the final electron acceptor and is reduced to water. Coenzyme Q (CoQ) is one of the main electron carriers in ETC. It takes part in generating the mitochondrial membrane potential, and is associated with the activities of complexes I, II and III.^{34,35} The final element of OXPHOS is ATP synthase, where ATP is generated.³⁶ Mitochondrial allostatic overload and the functional and structural alterations in mitochondria due to the cumulative burden of lifetime psychological and physiological stress might lead to a less efficient OXPHOS, which might be compensated by upregulating glycolytic pathways, leading to more lactic acid production.³⁷

Reactive oxygen species (ROS) are produced in the complex I and III of ETC as a by-product. Although ROS are necessary for normal physiological processes such as signaling, excess ROS can damage various cellular components and need to be controlled by the cellular antioxidant system. The energy production process is tightly regulated, as any deviation from optimal function tends to increase the production of ROS. As any failure on the part of the antioxidant system can lead to cellular damage, including the lipid membrane of mitochondria, the end result of the antioxidant system overload, namely oxidative stress, can be cellular death.³⁸

A process that highly influences MB is the generation of new mitochondria, namely mitochondrial biogenesis. Its main regulator is the peroxisome proliferator activator receptor gamma-coactivator 1 α (PGC-1 α).³⁹ There is a tight balance between mitochondrial biogenesis and mitophagy, the process to eliminate damaged mitochondria. This balance can be disrupted

by aging or mitochondrial allostatic overload.^{37,40} Mitochondrial dynamics are also crucial to regulate MB. Mitochondrial fusion, the merging of two mitochondria to form one tubular structure, promotes OXPHOS and leads slightly damaged mitochondria to be used by sharing proteins of healthy mitochondria after merging. On the other hand, mitochondrial fission, forming two sister mitochondria from a single one, promotes mitophagy.⁴¹ The balance between fusion and fission can also shift in favour of fission by mitochondrial allostatic overload.³⁷ Alterations in mitochondrial dynamics can also lead to morphological changes in mitochondria, such as the formation of a donut shape due to abnormal fusion processes.⁴²

Evidence for the CMB model: The link of MB with the g and p factor

Since MB is relevant for the functioning of each cerebral cell and can, thus, affect many higher-order biological mechanisms of cerebral function, its importance for general cerebral function is plausible. Higher-order mechanisms that are affected through MB include neurotransmitter systems and synaptic plasticity but also the functioning of the stress response including the hypothalamic-pituitary-adrenal and the sympathetic-adreno-medullary axis.^{11,43}

Multiple studies found that MB is related to measures of p such as depressive symptoms, and borderline symptom severity.⁴⁴⁻⁴⁷ Similarly, MB has been shown to be linked to measures of g such as working memory, episodic memory, mild cognitive impairment, general intelligence, and self- and clinician-rated cognitive difficulties.^{44,47-51} More specifically, major depressive disorder, loss of energy and fatigue as well as subjective concentration problems and mild cognitive impairment were associated with reduced mitochondrial respiration in human peripheral blood mononuclear cells.^{44,50} Better working memory was associated with a higher number of mitochondria per presynaptic bouton of the monkey's dorsolateral prefrontal cortex.⁴⁸ Conversely, the frequency of boutons with dysfunctional donut-shaped mitochondria was negatively related to working memory in monkeys.⁴⁸

Third, the shared risk factors of g and p affect MB. They can be clustered in behavioral, stress-related and biological risk factors. The behavioural risk factors of g and p that affect MB include physical inactivity and a Western pro-inflammatory diet.⁵²⁻⁵⁴ The stress-related risk factors affecting MB includes a high trauma load and childhood maltreatment.^{3,55-58} Childhood maltreatment was related to increased mitochondrial respiration and density, lower cognitive performance, and higher general psychopathology.^{3,55,58} In addition, the biological risk factors of g and p are linked with MB, which includes low-grade inflammation, oxidative stress, carnitine, lack of micronutrients such as Coenzyme Q10, folic acid, vitamin deficiencies,

hyperhomocysteinemia, low polunsaturated fatty acids and impaired cardiac autonomic nervous system.^{33,59-69}

Finally, the dysregulation of MB plays an important role in biologically defined cerebral diseases that are phenotypically linked with g and p factor impairment. These include Alzheimer's disease, multiple sclerosis, and phenylketonuria.⁷⁰⁻⁷⁴

5. Implications of the CMB model

The CMB model enables a pure assessment of the functional domains and hierarchical levels. Therefore, it can reveal the link of each domain within different hierarchical levels with risk factors (e.g., childhood maltreatment and vitamin deficiencies), biomarkers (e.g., genes, amyloid/tau pathology, white matter integrity or cortical thickness), treatments (e.g., psychotherapy or pharmacotherapy) and clinical outcomes (e.g., suicide, use of welfare benefits and medication, and work performance) (see Figure 3). To assess these links, the variance due to higher-order factors needs to be extracted with bi- or tri-factor models.³ In the following, the resulting implications are explained in detail by the use of specific examples.

Caspi et al. showed that agreeableness is associated with less internalizing ($r = -0.22$), externalizing ($r = -0.32$) and thought disorders ($r = -0.30$).³ However, using a bi-factor model to extract the shared variance due to the p factor, demonstrated that higher agreeableness was linked (i) with a lower p factor ($r = -0.31$), (ii) with a lower externalizing factor ($r = -0.18$) and, importantly, (iii) with a higher internalizing factor ($r = 0.13$; the direction of the link reversed after accounting for p). Without accounting for the general psychopathology, the positive link of agreeableness with internalizing syndromes and the additional negative link with externalizing disorder cannot be revealed. Conway et al. reviews the evidence for this rationale within the HiTOP model.⁷⁵

What does this rationale mean for the CMB model? The model extends previous p and g factor models by adding a novel highest-level latent factor. We suggest that this approach has two additional implications. First, it can reveal the link of the general factor of cerebral function with risk factors, biomarkers, treatments, and clinical outcomes (see Figure 3). Second, by modelling the variance in manifest measures that is due to the c factor, a pure measure of p and g and their subdomains can be revealed. This enables an unbiased estimate of the link of these factors with p, g and their subdomains.

Below we provide examples with regard to childhood maltreatment as a risk factor, cortical thickness as a brain biomarker, dominantly inherited Alzheimer's disease as a genetic disorder, and different potential treatment responses. Caspi et al. showed that childhood maltreatment is associated with internalizing, externalizing and thought disorders if the p factor is not accounted for.³ After accounting for p, this higher-order factor is positively associated with childhood maltreatment, without any further links with its subdomains. As childhood maltreatment is also linked with the g factor it is possible that also the higher-order c factor may be affected.⁵⁸ Thus, using the CMB model approach would advance our understanding of the aversive effects of childhood maltreatment: How much does it impair general cerebral function and to what degree are impairments specific to p or g. Modelling the c factor is necessary to gain this knowledge.

With respect to biomarkers, cortical thickness is associated with measures of p and g, a finding that may be fully or partly explained by a link of cortical thickness with the c factor.^{76,77} After accounting for the variance explained by the c factor, distinct links for g and p may be revealed (e.g., thickness of the dorsolateral prefrontal cortex for g and orbitofrontal cortical thickness for p). Without modelling c, the overall cortical thickness would be misleadingly attributed to p and g, and the distinct alterations of g and p may remain undetected.^{76,77} Transdiagnostic and cross-disorder studies that model c are necessary to understand these links.⁷⁸ With respect to genetic disorders such as familial Alzheimer's disease, it could be shown that both personality and cognition is affected in a similar temporal pattern.^{79,80} This co-occurrence of p factor and g factor symptoms might be explained by changes in the c factor. Modelling the c factor could reveal the affected domains of cerebral function in a pure way. For example, it might reveal c factor changes with additional episodic memory changes in patients with dominantly inherited Alzheimer's disease. Revealing the pattern of Alzheimer-related impairment in c, p, g and its subdomains may enable an earlier diagnosis and treatment of the disease in the sporadic late-onset form.

Here, we demonstrate a hypothetical example of the model implications for understanding treatment effects. We might reveal that treatment A (e.g., physical exercise) may improve the c factor with a small effect size, without specific effects on p, g and their subdomains. Treatment B (e.g., cognitive-behavioural therapy for depression) may improve not the p factor but the internalizing spectrum with a medium effect size and additionally symptoms of distress with an additional small effect size. Treatment C (e.g., psychodynamic therapy) may improve p with a small effect size, without any additional effect on internalizing and externalizing spectra. Treatment D (e.g., electro-convulsive therapy) may improve the p factor or some of its

subdomains for a specific period but may deteriorate g or the c factor in the long-term. Evidence about treatment effects on different levels of cerebral function enables a more accurate view on their benefits. We believe that this evidence may result in optimal combinations of fast-acting, short-term symptom-specific treatments with rather large effect sizes, and slow-acting, long-term general factor treatments with rather small effect sizes. Symptom-specific treatments may improve short-term psychosocial functioning, and general factor treatments may improve general cerebral health, preventing symptom relapses and the occurrence of a wide range of symptoms that are not the focus of the current psychosocial problem. We assume that many treatments that affect general factors have smaller effect sizes and act more slowly than treatments that benefit specific symptoms. Therefore, research aiming to reveal general factor effects need (i) larger sample sizes, (ii) longer follow-up periods and (iii) more extensive assessment batteries to cover all symptoms. These three issues result in much higher research costs that are necessary to demonstrate efficacy of general factor treatments in contrast to specific-symptom treatments and put the former treatment in a systematic disadvantage. The CMB model is important to understand the problem of this research bias in favour of specific-symptom treatment. We propose that because of this inherent bias, regulations and guidelines to evaluate treatment effects on different levels of the hierarchy are necessary.

With regard to clinical outcomes (e.g., suicidality, use of medication and social welfare benefits) modelling the c factor may have advantages. For example, a large-scale study from Sweden revealed that most clinical outcomes are predicted by both p and g, even after statistically accounting for each other.¹⁷ This means that both general factors have specific, non-overlapping relations with important clinical outcomes. This has two implications. First, assessment of both general factors seems to be relevant in psychiatric disorders to estimate treatment requirement and costs that play a role in reimbursement considerations. A patient with a c factor impairment—or a combined p and g factor impairment—may need a costlier treatment than a patient with a specific p factor impairment without a g factor impairment. Second, by modelling the c factor, current findings could be extended by adding the link of the c factor beyond the specific links of p and g with clinical outcomes. Adding this link may improve prognosis and, hence, treatment planning. Taken together, hierarchical and dimensional models that assess the c factor and its subdomains may transform research and eventually clinical practice.

Figure 3 - Revealing variables linked to the c factor model domains. The relationship between each model domain with risk factors, biomarkers, treatment effects, and real world clinical outcomes can be revealed, as the model provides a pure measurement of c, p, g and its subdomains. Subdomains of p and g (see Figure 1 and 2) are not depicted for reasons of simplicity. c = c factor or general cerebral function; g = g factor or general intelligence; M = manifest variable; p = p factor or general psychopathology

6. Limitations of g and p factor measures

Measures of g and p may be stronger related as currently expected. Currently, the gold standard for assessment of the g factor is based on objective behavioral measures, while gold standards for assessment of the p factor are based on self-ratings or clinician-ratings. This methodological differences in measurement of g and p may lead to an underestimation of the true co-variation. To solve this issue, both p and g should be measured with all three potential approaches. Thus, it is possible to determine the amount of variance due to a method factor (self-rating, other-ratings, objective behaviors) or due to a cerebral function factor such as c, p and g. That means, self-rated, other-rated, and objective behavior measures should be used for both p and g in the same sample.

7. Conclusion

The c factor represents the highest-order in the taxonomy of cerebral function by integrating models of p (e.g., HiTOP) with models of g (e.g., BIS). Bi- or tri-factor structural equation models enable a pure, decomposed assessment of all domains and hierarchical levels such as the highest-order factor c, the second-order factors g and p, and the third-order factors (e.g., internalizing, externalizing symptoms, executive function, and episodic memory). A pure, decomposed assessment of all model domains and levels may transform many areas of research

and clinical practice in a similar way as dimensional and hierarchical p factor and g factor models.⁷⁵ It may pave the way to detect risk factors, biomarkers, treatment effects and clinical outcomes of all domains and hierarchical levels of cerebral function. Eventually, the impaired general and specific domains of an individual help to reveal the respective biological and psychosocial determinants that can be tackled using personalized and evidence-based treatments. We propose that MB may be one biological mechanism responsible for the shared variance between p and g.

References

- 1 Spearman, C. "General Intelligence" Objectively Determined and Measured. (1961).
- 2 Wolf, A. W. *et al.* Associations among major psychiatric diagnoses. *Journal of Consulting and Clinical Psychology* **56**, 292-294, doi:10.1037/0022-006X.56.2.292 (1988).
- 3 Caspi, A. *et al.* The p Factor One General Psychopathology Factor in the Structure of Psychiatric Disorders? *Clinical Psychological Science* (2014).
- 4 Lahey, B. B. *et al.* Is there a general factor of prevalent psychopathology during adulthood? *J. Abnorm. Psychol.* **121**, 971-977, doi:10.1037/a0028355 (2012).
- 5 Kotov, R. *et al.* The Hierarchical Taxonomy of Psychopathology (HiTOP): A dimensional alternative to traditional nosologies. *J. Abnorm. Psychol.* **126**, 454-477, doi:10.1037/abn0000258 (2017).
- 6 Caemmerer, J. M., Keith, T. Z. & Reynolds, M. R. Beyond individual intelligence tests: Application of Cattell-Horn-Carroll Theory. *Intelligence* **79**, 101433, doi:<https://doi.org/10.1016/j.intell.2020.101433> (2020).
- 7 Kotov, R. *et al.* The Hierarchical Taxonomy of Psychopathology (HiTOP): A Quantitative Nosology Based on Consensus of Evidence. *Annual Review of Clinical Psychology* **17**, 83-108, doi:10.1146/annurev-clinpsy-081219-093304 (2021).
- 8 Geary, D. C. Efficiency of mitochondrial functioning as the fundamental biological mechanism of general intelligence (g). *Psychol. Rev.* **125**, 1028-1050, doi:10.1037/rev0000124 (2018).
- 9 Debatin, T. A Revised Mental Energy Hypothesis of the g Factor in Light of Recent Neuroscience. *Rev. Gen. Psychol.* **23**, 201-210, doi:10.1177/1089268019832846 (2019).
- 10 Karabatsiakakis, A. & Schönfeldt-Lecuona, C. Depression, mitochondrial bioenergetics, and electroconvulsive therapy: a new approach towards personalized medicine in psychiatric treatment - a short review and current perspective. *Translational Psychiatry* **10**, 226, doi:10.1038/s41398-020-00901-7 (2020).
- 11 Picard, M., McEwen, B. S., Epel, E. S. & Sandi, C. An energetic view of stress: Focus on mitochondria. *Front. Neuroendocrinol.* **49**, 72-85, doi:10.1016/j.yfrne.2018.01.001 (2018).
- 12 Fusar-Poli, P. *et al.* Transdiagnostic psychiatry: a systematic review. *World Psychiatry* **18**, 192-207 (2019).
- 13 van der Linden, D., te Nijenhuis, J. & Bakker, A. B. The General Factor of Personality: A meta-analysis of Big Five intercorrelations and a criterion-related validity study. *Journal of Research in Personality* **44**, 315-327, doi:<https://doi.org/10.1016/j.jrp.2010.03.003> (2010).

- 14 Oltmanns, J. R., Smith, G. T., Oltmanns, T. F. & Widiger, T. A. General Factors of Psychopathology, Personality, and Personality Disorder: Across Domain Comparisons. *Clinical Psychological Science* **6**, 581-589, doi:10.1177/2167702617750150 (2018).
- 15 Hörz-Sagstetter, S. *et al.* A Bifactor Model of Personality Organization. *Journal of Personality Assessment* **103**, 149-160, doi:10.1080/00223891.2019.1705463 (2021).
- 16 Jauk, E. & Ehrental, J. C. Self-Reported Levels of Personality Functioning from the Operationalized Psychodynamic Diagnosis (OPD) System and Emotional Intelligence Likely Assess the Same Latent Construct. *Journal of Personality Assessment*, 1-15, doi:10.1080/00223891.2020.1775089 (2020).
- 17 Pettersson, E., Larsson, H., D'Onofrio, B. M., Bölte, S. & Lichtenstein, P. The general factor of psychopathology: a comparison with the general factor of intelligence with respect to magnitude and predictive validity. *World Psychiatry* **19**, 206-213, doi:<https://doi.org/10.1002/wps.20763> (2020).
- 18 Süß, H.-M. & Beauducel, A. Modeling the construct validity of the Berlin Intelligence Structure Model. *Estudos de Psicologia (Campinas)* **32**, 13-25, doi:10.1590/0103-166X2015000100002 (2015).
- 19 Küster, O. C. *et al.* Cognitive change is more positively associated with an active lifestyle than with training interventions in older adults at risk of dementia: A controlled interventional clinical trial. *BMC Psychiatry* **16**, 315, doi:10.1186/s12888-016-1018-z (2016).
- 20 Murray, A. L. & Johnson, W. The limitations of model fit in comparing the bi-factor versus higher-order models of human cognitive ability structure. *Intelligence* **41**, 407-422, doi:<https://doi.org/10.1016/j.intell.2013.06.004> (2013).
- 21 Gatchel, J. R. *et al.* Longitudinal Association of Depression Symptoms With Cognition and Cortical Amyloid Among Community-Dwelling Older Adults. *JAMA Network Open* **2**, e198964-e198964, doi:10.1001/jamanetworkopen.2019.8964 (2019).
- 22 Hammar, Å. & Årdal, G. Cognitive functioning in major depression-a summary. *Front. Hum. Neurosci.* **3**, 26 (2009).
- 23 Kalkstein, S., Hurford, I. & Gur, R. C. in *Behavioral Neurobiology of Schizophrenia and Its Treatment* (ed Neal R. Swerdlow) 373-390 (Springer Berlin Heidelberg, 2010).
- 24 Parslow, R. A. & Jorm, A. F. Pretrauma and posttrauma neurocognitive functioning and PTSD symptoms in a community sample of young adults. *Am. J. Psychiatry* **164**, 509-515, doi:10.1176/ajp.2007.164.3.509 (2007).
- 25 Lyketsos, C. G. *et al.* Prevalence of Neuropsychiatric Symptoms in Dementia and Mild Cognitive Impairment Results From the Cardiovascular Health Study. *JAMA* **288**, 1475-1483, doi:10.1001/jama.288.12.1475 (2002).
- 26 Singh-Manoux, A., Dugravot, A., Fournier, A. & *et al.* Trajectories of depressive symptoms before diagnosis of dementia: A 28-year follow-up study. *JAMA Psychiatry*, doi:10.1001/jamapsychiatry.2017.0660 (2017).
- 27 Wang, W.-W., Liu, X.-L., Ruan, Y., Wang, L. & Bao, T.-H. Depression was associated with apolipoprotein E ϵ 4 allele polymorphism: A meta-analysis. *Iran J Basic Med Sci* **22**, 112-117, doi:10.22038/ijbms.2018.30825.7436 (2019).
- 28 Storandt, M., Balota, D. A., Aschenbrenner, A. J. & Morris, J. C. Clinical and psychological characteristics of the initial cohort of the Dominantly Inherited Alzheimer Network (DIAN). *Neuropsychology* **28**, 19 (2014).
- 29 Penner, I.-K. Evaluation of cognition and fatigue in multiple sclerosis: daily practice and future directions. *Acta Neurol. Scand.* **134**, 19-23, doi:<https://doi.org/10.1111/ane.12651> (2016).
- 30 Brumm, V. L., Bilder, D. & Waisbren, S. E. Psychiatric symptoms and disorders in phenylketonuria. *Molecular Genetics and Metabolism* **99**, S59-S63, doi:<https://doi.org/10.1016/j.ymgme.2009.10.182> (2010).

- 31 Janzen, D. & Nguyen, M. Beyond executive function: Non-executive cognitive abilities in individuals with PKU. *Molecular Genetics and Metabolism* **99**, S47-S51, doi:<https://doi.org/10.1016/j.ymgme.2009.10.009> (2010).
- 32 Hyder, F., Rothman, D. L. & Bennett, M. R. Cortical energy demands of signaling and nonsignaling components in brain are conserved across mammalian species and activity levels. *Proc Natl Acad Sci U S A* **110**, 3549-3554, doi:10.1073/pnas.1214912110 (2013).
- 33 Wesselink, E., Koekkoek, W. A. C., Grefte, S., Witkamp, R. F. & van Zanten, A. R. H. Feeding mitochondria: Potential role of nutritional components to improve critical illness convalescence. *Clin. Nutr.* **38**, 982-995, doi:<https://doi.org/10.1016/j.clnu.2018.08.032> (2019).
- 34 Shults, C. W., Haas, R. H., Passov, D. & Beal, M. F. Coenzyme Q10 levels correlate with the activities of complexes I and II/III in mitochondria from parkinsonian and nonparkinsonian subjects. *Ann. Neurol.* **42**, 261-264, doi:<https://doi.org/10.1002/ana.410420221> (1997).
- 35 Alcázar-Fabra, M., Navas, P. & Brea-Calvo, G. Coenzyme Q biosynthesis and its role in the respiratory chain structure. *Biochim. Biophys. Acta* **1857**, 1073-1078, doi:<https://doi.org/10.1016/j.bbabi.2016.03.010> (2016).
- 36 Dashty, M. A quick look at biochemistry: Carbohydrate metabolism. *Clin. Biochem.* **46**, 1339-1352, doi:<https://doi.org/10.1016/j.clinbiochem.2013.04.027> (2013).
- 37 Picard, M., Juster, R. P. & McEwen, B. S. Mitochondrial allostatic load puts the 'gluc' back in glucocorticoids. *Nat Rev Endocrinol* **10**, 303-310, doi:10.1038/nrendo.2014.22 (2014).
- 38 Galley, H. F. Oxidative stress and mitochondrial dysfunction in sepsis. *Br. J. Anaesth.* **107**, 57-64, doi:10.1093/bja/aer093 (2011).
- 39 Dominy, J. E. & Puigserver, P. Mitochondrial biogenesis through activation of nuclear signaling proteins. *Cold Spring Harb. Perspect. Biol.* **5**, doi:10.1101/cshperspect.a015008 (2013).
- 40 Palikaras, K., Lionaki, E. & Tavernarakis, N. Balancing mitochondrial biogenesis and mitophagy to maintain energy metabolism homeostasis. *Cell Death Differ* **22**, 1399-1401, doi:10.1038/cdd.2015.86 (2015).
- 41 Tilokani, L., Nagashima, S., Paupe, V. & Prudent, J. Mitochondrial dynamics: overview of molecular mechanisms. *Essays Biochem.* **62**, 341-360, doi:10.1042/ebc20170104 (2018).
- 42 Liu, X. & Hajnoczky, G. Altered fusion dynamics underlie unique morphological changes in mitochondria during hypoxia-reoxygenation stress. *Cell Death Differ.* **18**, 1561-1572 (2011).
- 43 Todorova, V. & Blokland, A. Mitochondria and Synaptic Plasticity in the Mature and Aging Nervous System. *Curr. Neuropharmacol.* **15**, 166-173 (2017).
- 44 Karabatsiakakis, A. *et al.* Mitochondrial respiration in peripheral blood mononuclear cells correlates with depressive subsymptoms and severity of major depression. *Transl Psychiatry* **4**, e397, doi:10.1038/tp.2014.44 (2014).
- 45 Anglin, R. Mitochondrial Dysfunction in Psychiatric Illness. *The Canadian Journal of Psychiatry* **61**, 444-445, doi:10.1177/0706743716646361 (2016).
- 46 Holper, L. *et al.* Brain cytochrome-c-oxidase as a marker of mitochondrial function: A pilot study in major depression using NIRS. *Depression and Anxiety* **36**, 766-779, doi:<https://doi.org/10.1002/da.22913> (2019).
- 47 Rappel, M. *et al.* Abstract # 1803 Mitochondrial respiration in peripheral blood mononuclear cells of individuals with borderline personality disorder. *Brain, Behavior, and Immunity* **57**, e27, doi:<https://doi.org/10.1016/j.bbi.2016.07.091> (2016).

- 48 Hara, Y. *et al.* Presynaptic mitochondrial morphology in monkey prefrontal cortex correlates with working memory and is improved with estrogen treatment. *Proc Natl Acad Sci U S A* **111**, 486-491, doi:10.1073/pnas.1311310110 (2014).
- 49 Olesen, M. A., Torres, A. K., Jara, C., Murphy, M. P. & Tapia-Rojas, C. Premature synaptic mitochondrial dysfunction in the hippocampus during aging contributes to memory loss. *Redox Biology* **34**, 101558, doi:<https://doi.org/10.1016/j.redox.2020.101558> (2020).
- 50 Apaijai, N. *et al.* Cognitive impairment is associated with mitochondrial dysfunction in peripheral blood mononuclear cells of elderly population. *Sci. Rep.* **10**, 21400, doi:10.1038/s41598-020-78551-4 (2020).
- 51 Bijmens, E. M. *et al.* Placental mitochondrial DNA content is associated with childhood intelligence. *J. Transl. Med.* **17**, 1-9 (2019).
- 52 Brand, S. *et al.* Influence of Regular Physical Activity on Mitochondrial Activity and Symptoms of Burnout—An Interventional Pilot Study. *Journal of Clinical Medicine* **9**, 667 (2020).
- 53 Park, H. S. *et al.* Physical exercise prevents cognitive impairment by enhancing hippocampal neuroplasticity and mitochondrial function in doxorubicin-induced chemobrain. *Neuropharmacology* **133**, 451-461, doi:10.1016/j.neuropharm.2018.02.013 (2018).
- 54 Valls-Pedret, C., Sala-Vila, A., Serra-Mir, M. & *et al.* Mediterranean diet and age-related cognitive decline: A randomized clinical trial. *JAMA Internal Medicine* **175**, 1094-1103, doi:10.1001/jamainternmed.2015.1668 (2015).
- 55 Gump, A. M. *et al.* Childhood maltreatment is associated with changes in mitochondrial bioenergetics in maternal, but not in neonatal immune cells. *Proc Natl Acad Sci U S A* **117**, 24778-24784, doi:10.1073/pnas.2005885117 (2020).
- 56 Boeck, C. *et al.* Inflammation in adult women with a history of child maltreatment: The involvement of mitochondrial alterations and oxidative stress. *Mitochondrion* **30**, 197-207, doi:<https://doi.org/10.1016/j.mito.2016.08.006> (2016).
- 57 Gerke, J. *et al.* Childhood maltreatment as risk factor for lifetime depression: The role of different types of experiences and sensitive periods. *Mental Health & Prevention* **10**, 56-65 (2018).
- 58 Cowell, R. A., Cicchetti, D., Rogosch, F. A. & Toth, S. L. Childhood maltreatment and its effect on neurocognitive functioning: Timing and chronicity matter. *Dev Psychopathol* **27**, 521-533, doi:10.1017/s0954579415000139 (2015).
- 59 Momiyama, Y. *et al.* Cardiac Autonomic Nervous Dysfunction in Diabetic Patients With a Mitochondrial DNA Mutation. *Assessment by heart rate variability* **25**, 2308-2313, doi:10.2337/diacare.25.12.2308 (2002).
- 60 Forte, G., Favieri, F. & Casagrande, M. Heart Rate Variability and Cognitive Function: A Systematic Review. *Front. Neurosci.* **13**, doi:10.3389/fnins.2019.00710 (2019).
- 61 Beauchaine, T. P. & Thayer, J. F. Heart rate variability as a transdiagnostic biomarker of psychopathology. *Int. J. Psychophysiol.* **98**, 338-350, doi:10.1016/j.ijpsycho.2015.08.004 (2015).
- 62 Tao, Q. *et al.* Association of Chronic Low-grade Inflammation With Risk of Alzheimer Disease in ApoE4 Carriers. *JAMA Network Open* **1**, e183597-e183597, doi:10.1001/jamanetworkopen.2018.3597 (2018).
- 63 Osimo, E. F., Baxter, L. J., Lewis, G., Jones, P. B. & Khandaker, G. M. Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels. *Psychol. Med.* **49**, 1958-1970, doi:10.1017/S0033291719001454 (2019).
- 64 Leonard, B. & Maes, M. Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels

- and concomitants play a role in the pathophysiology of unipolar depression. *Neurosci. Biobehav. Rev.* **36**, 764-785 (2012).
- 65 Bennett, S., Grant, M. M. & Aldred, S. Oxidative stress in vascular dementia and Alzheimer's disease: a common pathology. *Journal of Alzheimer's Disease* **17**, 245-257 (2009).
 - 66 Wang, S.-M. *et al.* A review of current evidence for acetyl-L-carnitine in the treatment of depression. *J. Psychiatr. Res.* **53**, 30-37 (2014).
 - 67 Maes, M. *et al.* Lower plasma Coenzyme Q10 in depression: a marker for treatment resistance and chronic fatigue in depression and a risk factor to cardiovascular disorder in that illness. *Neuro Endocrinol. Lett.* **30**, 462-469 (2009).
 - 68 Sanoobar, M., Dehghan, P., Khalili, M., Azimi, A. & Seifar, F. Coenzyme Q10 as a treatment for fatigue and depression in multiple sclerosis patients: A double blind randomized clinical trial. *Nutr. Neurosci.* **19**, 138-143, doi:10.1179/1476830515y.00000000002 (2016).
 - 69 Das, U. N. Folic acid and polyunsaturated fatty acids improve cognitive function and prevent depression, dementia, and Alzheimer's disease—But how and why? *Prostaglandins, Leukotrienes and Essential Fatty Acids* **78**, 11-19, doi:<https://doi.org/10.1016/j.plefa.2007.10.006> (2008).
 - 70 Wyse, A. T. S., Dos Santos, T. M., Seminotti, B. & Leipnitz, G. Insights from Animal Models on the Pathophysiology of Hyperphenylalaninemia: Role of Mitochondrial Dysfunction, Oxidative Stress and Inflammation. *Mol. Neurobiol.* **58**, 2897-2909, doi:10.1007/s12035-021-02304-1 (2021).
 - 71 Holper, L., Ben-Shachar, D. & Mann, J. J. Multivariate meta-analyses of mitochondrial complex I and IV in major depressive disorder, bipolar disorder, schizophrenia, Alzheimer disease, and Parkinson disease. *Neuropsychopharmacology* **44**, 837-849, doi:10.1038/s41386-018-0090-0 (2019).
 - 72 Tang, J., Oliveros, A. & Jang, M.-H. Dysfunctional Mitochondrial Bioenergetics and Synaptic Degeneration in Alzheimer Disease. *Int. Neurol.* **23**, S5-S10, doi:10.5213/inj.1938036.018 (2019).
 - 73 Leuner, K. *et al.* Peripheral mitochondrial dysfunction in Alzheimer's disease: focus on lymphocytes. *Mol. Neurobiol.* **46**, 194-204, doi:10.1007/s12035-012-8300-y (2012).
 - 74 Barcelos, I. P. d., Troxell, R. M. & Graves, J. S. Mitochondrial Dysfunction and Multiple Sclerosis. *Biology (Basel)* **8**, 37, doi:10.3390/biology8020037 (2019).
 - 75 Conway, C. C. *et al.* A Hierarchical Taxonomy of Psychopathology Can Transform Mental Health Research. *Perspect. Psychol. Sci.* **14**, 419-436, doi:10.1177/1745691618810696 (2019).
 - 76 Romer, A. L. *et al.* Pervasively Thinner Neocortex as a Transdiagnostic Feature of General Psychopathology. *Am. J. Psychiatry* **178**, 174-182, doi:10.1176/appi.ajp.2020.19090934 (2020).
 - 77 Menary, K. *et al.* Associations between cortical thickness and general intelligence in children, adolescents and young adults. *Intelligence* **41**, 597-606 (2013).
 - 78 Opel, N. *et al.* Cross-Disorder Analysis of Brain Structural Abnormalities in Six Major Psychiatric Disorders – A Secondary Analysis of Mega- and Meta-Analytical Findings from the ENIGMA Consortium. *Biol. Psychiatry*, doi:10.1016/j.biopsych.2020.04.027.
 - 79 Storandt, M., Balota, D. A., Aschenbrenner, A. J. & Morris, J. C. Clinical and Psychological Characteristics of Initial Cohort of the Dominantly Inherited Alzheimer Network (DIAN). *Neuropsychology* **28**, 10.1037/neu0000030, doi:10.1037/neu0000030 (2014).

- 80 Bateman, R. J. *et al.* Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *New England Journal of Medicine* **367**, 795-804, doi:10.1056/NEJMoa1202753 (2012).