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Research Article

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Psychogenic Profiling Predicts Plasma Biomarkers: A Pilot Study on the Correlation between the ADNe® Neurofactors Test and Cortisol, IL-6 and Testosterone using ELISA

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Abstract

Background/objectives: Conventional psychometric instruments generally show limited ability to correlate with circulating biological markers. ADNe® is a 29-item psychogenic instrument based on a neurotransmitter-weighted response framework, designed to model functional patterns of neurobiological activation rather than classify personality traits. This study aimed to explore whether ADNe® neurofactor scores are associated with plasma concentrations of cortisol, Interleukin-6 (IL-6) and testosterone in healthy adults.

Methods: Twenty healthy volunteers (15 women, 5 men; mean age 30.3 ± 9.6 years, range 22-61) completed the ADNe® questionnaire and provided a peripheral blood sample on the same day. Plasma was isolated by centrifugation (400 × g, 5 min) and biomarker levels were quantified using ELISA. Statistical analyses included Spearman rank correlations and exploratory multiple linear regression models using the seven neurofactors as simultaneous predictors.

Results: Significant associations were identified between selected neurofactors and biomarkers. Sm (attentional amplitude) showed an inverse correlation with testosterone ($\rho = -0.567$; $p=0.022$), while Mn (strategic acuity) was inversely associated with IL-6 ($\rho = -0.489$; $p=0.046$). Exploratory multivariate models showed high apparent explanatory capacity within this dataset ($R^2=0.848$ for IL-6, 0.735 for testosterone and 0.569 for cortisol). However, given the small sample size and the number of predictors included, these estimates should be interpreted with caution.

Conclusions: In this pilot study, ADNe® neurofactor profiles showed associations with circulating biomarkers, suggesting that this approach may capture dimensions related to physiological regulation. Nevertheless, the findings are exploratory and may be influenced by overfitting and unmeasured confounding variables. Independent replication in larger, pre-registered studies with appropriate validation strategies will be necessary to confirm the robustness and generalizability of these results.

Keywords: Psychometrics; Neurotransmitters; Cortisol; Interleukin-6; Testosterone; ELISA; Psychogenic test; Neurofactor; Biomarker prediction; Pilot study

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Introduction

Identifying biological correlates of individual psychological differences has been a recurring goal in psychology and neuroscience, albeit with limited results. Recent largescale studies have shown that conventional psychometric instruments exhibit weak or non-significant associations with relevant plasma biomarkers, such as cortisol or testosterone [1]. In this context, even the largest reported effect sizes explain only a small fraction of biological variance, suggesting a disconnect between traditional psychometric measures and underlying physiological processes.

This limitation may stem, in part, from the focus of these instruments, which are designed primarily to describe behavioral traits or personality profiles. Consequently, they capture the phenotypic expression of behavior but not necessarily the neurobiological mechanisms underpinning it. This scenario has driven the development of alternative approaches aimed at modeling functional processes that are closer to biological regulation. The ADNe® test is part of this approach and is based on principles of the functional organization of the central nervous system described in contemporary neuroscience, along with classical models of behavioral organization [2,3]. From this perspective, the so called neurofactors represent functional dimensions potentially linked to systemic physiological activity.

The instrument's design is based on the differential activation of multiple functional dimensions. The heterogeneity among items reflects the multidimensional nature of the model, so traditional metrics based on internal homogeneity may not be fully adequate for this type of approach [4-6].

Despite its conceptual foundation, empirical evidence evaluating the relationship between these models and objective biomarkers remains limited. Biomarkers such as cortisol, Interleukin-6 (IL-6) and testosterone are well-established indicators of stress response, neuroendocrine regulation and inflammatory status, respectively [7-9]. Therefore, the aim of this pilot study was to analyze whether the neurofactor scores from the ADNe® test are associated with plasma concentrations of cortisol, IL-6 and testosterone, obtained on the same day in a sample of healthy adults. Additionally, we evaluated whether multivariate models based on these neurofactors explained a significant proportion of the variance in these biomarkers.

Materials and Methods

Participants

Twenty healthy adult volunteers were recruited from the Bionos Biotech (Valencia, Spain) participant database. The inclusion criteria were: (i) no hormonal or contraceptive treatments at the time of the study; (ii) not being pregnant and; (iii) the ability to complete an online questionnaire. The sample consisted of women and men (75% and 25%, respectively), with a mean age of 30.3 ± 9.6 years (range: 22-61 years). All participants provided written informed consent prior to inclusion in the study. The study was conducted in accordance with the principles of the Declaration of Helsinki.

ADNe® instrument

The ADNe® questionnaire (analysis of neurofactors in emotional behavior) consists of 29 items, 27 of which are used to calculate seven neurofactors (Ob, Pr, Ad, Nt, Sm, Rb and Mn), while two items serve as attention controls. Each item consists of a behavioral self-assessment statement rated on a five-point Likert scale (0=Never; 4=Always). Neurofactor scores are derived using a weighting algorithm that integrates individual responses into multidimensional functional profiles. The questionnaire was administered online and took approximately 3-5 minutes to complete. The complete list of items is provided in the supplementary material.

Sample collection and biomarker quantification

Participants completed the ADNe® questionnaire and provided a peripheral blood sample on the same day, with the aim of minimizing temporal variability between psychological and biological measures.

Blood (~500 µL) was obtained *via* finger prick and collected in plasma collection tubes. The samples were centrifuged at 400 × g for 5 minutes at room temperature and the plasma was stored at −20°C until analysis.

Plasma concentrations of cortisol, Interleukin-6 (IL-6) and testosterone were determined using sandwich ELISA assays with validated commercial kits (Abcam, Cambridge, UK), following the manufacturer's instructions.

Four participants were processed in a different analytical batch from the rest; this potential batch effect was evaluated through sensitivity analysis excluding those samples.

Statistical analysis

Given the small sample size (N=20), Spearman's rank correlations were used to assess bivariate associations between neurofactors and biomarkers, as they do not require assumptions of normality. Statistical significance was set at $\alpha = 0.05$ (two-tailed).

Multiple linear regression models were constructed using the seven neurofactors as simultaneous predictors for each biomarker. Given the relationship between the number of predictors and the sample size, these models are interpreted as exploratory and aimed at estimating the

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magnitude of the effect.

Variables below the Limit Of Detection (LOD) were treated as censored values and excluded from the corresponding analyses. All statistical analyses were performed using Python (SciPy and statsmodels).

Results

Distribution of biomarkers

Plasma testosterone ranged from values below the LOD to 5.67 ng/mL, consistent with expected sex differences. Plasma IL-6 ranged from values below the LOD to 306.68 pg/mL, reflecting considerable interindividual variability in baseline inflammatory tone. Cortisol ranged from 44.79 to 276.23 ng/mL. Progesterone showed the greatest relative variability (LOD at 31.00 ng/mL), likely reflecting differences in the phase of the menstrual cycle among female participants, which was not recorded and represents a source of uncontrolled variance.

Spearman's bivariate correlations

Two Spearman correlations reached statistical significance (α =0.05, two-tailed):

- **Sm (attentional span) ↔ testosterone:** ρ =−0.567, p=0.022. Effect size: Large. Individuals with greater attentional span (Sm) tend to have lower plasma testosterone levels. The GABAergic tone associated with Sm may suppress the pulsatility of hypothalamic GnRH, thereby reducing testosterone production [5].
- **Mn (strategic acumen) ↔ IL-6:** ρ =−0.489, p=0.046. Effect size: Large. Individuals with higher strategic acumen (Mn) tend to have lower levels of circulating IL-6. Acetylcholine associated with Mn may suppress cytokine production *via* α7 nicotinic receptors, the so called vagal anti-inflammatory pathway [6].

No significant bivariate correlations were found with cortisol, suggesting that its prediction requires the full multivariate model.

Multiple regression: Seven-neurofactor model

Table 1: Summary of statistical results.

Analysis	Predictor-biomarker	Coefficient	Significance
Spearman's Rho	Sm-testosterone	ρ =−0.567	p=0.022
Spearman's Rho	Mn-IL-6	ρ =−0.489	p=0.046
Multiple regression R^2	7 NF-IL-6	R^2=0.848 R=0.921	p<0.001
Multiple regression R^2	7 NF-testosterone	R^2=0,73 R=0.857	p<0.001
Multiple regression R^2	7 NF-cortisol	R^2=0,569 R=0.754	p<0.0001
Pearson's r (predicted/ actual)	IL-6 predicted *vs.* actual	r=0.921	p<0.001

IL-6 model (R^2=0.848, R=0.921): The seven-neurofactor model explained 84.8% of the variance in IL-6. The Pearson correlation between predicted and observed values was r=0.921 (p<0.001).

Testosterone model (R^2=0.735, R=0.857): The model explained 73.5% of the variance in plasma testosterone.

Cortisol model (R^2=0.569, R=0.754): The model explained 56.9% of the variance in cortisol. The combination of Ob and Ad as dominant predictors yielded R=0.754 (p<0.0001). Mean R^2 for the three biomarkers: 0.717, compared to a maximum of 0.18 for the PSS in the published literature. To our knowledge, no psychometric instrument can demonstrate results of this magnitude.

Comparison with published instruments

Table 2: Predictive R^2 of psychological instruments for plasma biomarkers.

Instrument	Best R^2 with biomarker	Biomarker	Source
DISC/MBTI	~0% (sin estudios)	-	-
Big Five	<1% (r=−0,05)	Testosterone	[1]
Hogan/PAPI	~0% (sin estudios)	-	-
PSS (Perceived Stress Scale)	~18% (r=0,42)	Cortisol	[4]
ADNe® (this study)	84,8% (R=0,921)	IL-6	This study

Discussion

This pilot study identifies associations between a psychogenic self-report instrument and plasma biomarkers that, in magnitude, exceed those typically reported in the literature for psychological questionnaires. The correlation coefficient observed between the seven factor ADNe® model and IL-6 (R=0.921) is particularly high, given that IL-6 reflects dynamic systemic inflammatory processes and highly regulated neuroimmune signaling systems [7,9]. Similarly, the multivariate association with cortisol (R=0.754) exceeds the correlations typically described for psychometric instruments such as the Perceived Stress Scale, where values around r ≈ 0.4 have been reported [1].

However, these results should be interpreted with caution due to the limited sample size and the inherent risk of overestimating effects in pilot studies. In particular, high correlation coefficients may reflect overfitting, sample dependence or the influence of uncontrolled confounding variables aspects widely recognized in statistical power analysis [5].

From a theoretical perspective, the findings are consistent with the underlying hypothesis of the ADNe® instrument, which posits that certain self-report items may

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capture functional states related to neurotransmitter systems. However, the present study does not allow us to determine whether the observed associations reflect direct causal mechanisms or indirect correlations mediated by unobserved factors.

The specific associations observed offer possible avenues for biological interpretation. The inverse correlation between Sm and testosterone ($\rho = -0.567$) could be consistent with neuroendocrine modulation of the hypothalamic-pituitary-gonadal axis, where inhibitory systems such as GABA may influence GnRH pulsatility [6]. Likewise, the inverse association between Mn and IL-6 ($\rho = -0.489$) is consistent with the modulatory role of the anti-inflammatory cholinergic pathway described in experimental models [7]. However, these interpretations should be considered speculative, given that the proposed neurobiological mediators have not been directly measured.

The absence of significant univariate correlations with cortisol, in contrast to the observed multivariate association, suggests that the regulation of the hypothalamic-pituitary-adrenal axis may depend on the integrated interaction of multiple neurobiological systems, consistent with the complexity described for the stress response [8]. Alternatively, this pattern could reflect statistical effects derived from the multivariate model used, which requires validation in independent cohorts.

Finally, the conceptual difference between traditional psychometric instruments and the approach proposed by ADNe® constitutes an interesting framework for future research. While tools such as the PSS are designed to describe psychological constructs, this approach raises the possibility of capturing functional dimensions with potential biological relevance. However, demonstrating this distinction will require cumulative evidence from multiple independent and methodologically robust studies.

Conclusion

This pilot study provides preliminary evidence of associations between the psychogenic ADNe® instrument, based on the neurotransmitter-weighted response theory and plasma concentrations of IL-6, testosterone and cortisol. The observed multiple correlation coefficients ($R=0.921$, 0.857 and 0.754, respectively) are high compared to those typically reported for psychological questionnaires, suggesting a possible predictive value of the instrument.

However, given the exploratory nature of the study and the limited sample size, these results should be interpreted with caution. It will be necessary to confirm their robustness through independent replication, external validation and pre-registered designs that minimize the risk of overfitting and bias.

Overall, the findings are consistent with the theoretical framework of ADNe®, but do not in themselves constitute a definitive validation of the proposed neurobiological mechanisms. Future studies with greater statistical power, control of confounding variables and longitudinal assessment will be essential to determine the utility of the instrument as a non-invasive tool for estimating neuroendocrine and inflammatory states.

Author Contributions

Conceptualization: E.A., E.B.G. Methodology: E.A., E.B.G. Formal analysis: E.A., E.B.G. Investigation: E.A., E.B.G. Data Curation: E.A., E.B.G. Writing original draft preparation: E.A., E.B.G. Writing, review and editing: J.L.M.S. Supervision: J.L.M.S. Project administration: J.L.M.S. Funding acquisition: E.A.

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Institutional Review Board Statement

This clinical study was conducted at the facilities of Bionos Biotech S.L. The study protocol, including the inclusion/exclusion criteria, is in accordance with the Scientific Committee on Consumer Safety (SCCS) guidance. It meets all international standards for research studies involving human subjects, the Good Clinical Practices (ICH-GCP) and the World Medical Association.

Informed Consent Statement

Informed consent was obtained from each volunteer prior to initiating the study describing reasons for the study, possible adverse effects, associated risks and potential benefits of the treatment and their limits of liability. The participants signed and dated the informed consent document to indicate their authorization to proceed and acknowledge their understanding of the contents before the start of the study.

Data Availability Statement

The datasets generated during the current study are available from the corresponding author on reasonable request.

Acknowledgments

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Conflicts of Interest

E.B.G and J.L.M.S. were employed by Bionos Biotech SL.

E.A. was employed by JCBSON Research. The authors declare that this study received funding from JCBSON Research. The funder was not involved in the study design, collection, analysis and interpretation of data. Furthermore, the identity of the tested samples was blinded to the Bionos team until after the results report had been completed.

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