

Exhaustion and Wear-and-Tear as Distinct Components of Operational Fatigue: A Double-Blind, Placebo-Controlled Trial of L-Tyrosine Supplementation

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Abstract

Consequence of chronic stress in military personnel is often described via the term "operational fatigue," which may conflate two distinct phenomena: exhaustion and wear-and-tear (mental distancing). This study investigated whether these constructs reflect different psychophysiological pathways and tested L-tyrosine supplementation as a nonpharmacological recovery strategy. A cohort of 116 French military personnel was followed, split into a deployed group (Mali, Operation Barkhane) and a nondeployed control group, each further divided into placebo and L-tyrosine subgroups in a double-blind randomized design. Across four visits (predeployment, immediate return, one month, and three months post-return), participants completed the Burnout Assessment Tool and underwent blood sampling for amino acids and BDNF.

The results revealed that L-tyrosine reduced exhaustion scores in both the deployed and nondeployed groups, whereas wear-and-tear was unaffected by supplementation but was instead negatively correlated with tryptophan levels. BDNF decreased after deployment and rose three months later, an increase driven primarily by the L-tyrosine subgroup. These findings suggest that exhaustion is linked to catecholaminergic/dopaminergic depletion and BDNF-mediated sleep disruption, whereas wear-and-tear is related to serotonergic dysregulation. Distinguishing these two components of operational fatigue could refine personnel selection, training, and targeted interventions for burnout recovery.

Introduction

Military personnel engaged in overseas operations are subjected to a variety of environmental and psychophysiological stresses that can result in elevated levels of operational stress. This stress can result in what is known as "operational fatigue" [1] (Houel et al., 2015), which is traditionally interpreted as the consequence of a temporary depletion of biopsychological resources. In most cases, this fatigue is reversible after the mission, owing to recovery periods that combine rest, catch-up sleep, and a return to a normal daily routine. However, clinical observations suggest that these recovery mechanisms may prove insufficient in some individuals, leading to symptoms that persist beyond the expected timeframe. In certain situations, this state persists despite an apparent normalization of recovery parameters, such as sleep debt or exposure to stressors. Affected individuals report functional impairment, characterized by statements such as "I cannot do it anymore" or "I don't want to do it anymore" despite the absence of objective clinical signs that would substantiate a diagnosis of formal medical unfitness. The discrepancy between subjective experience and standard clinical assessment constitutes a significant challenge in evaluating operational capacity.

This incomplete recovery prompts inquiries into the standards for medical clearance to resume duty and the underlying pathophysiological processes. In instances where a state of exhaustion persists despite apparent recovery, the hypothesis of an operational wear-and-tear process may be proposed. This process would not be limited to a quantitative depletion of resources but would also involve an impairment of their functional accessibility, reflecting difficulty in effectively mobilizing capacities that

are otherwise preserved at the organic level. Indeed, operational environments are characterized by an accumulation of physical, cognitive, and emotional stressors, the effects of which are intense, prolonged, and cumulative (Frueh et al., 2020). These stresses disrupt individual and collective adaptive mechanisms, thereby placing constant demands on the body's regulatory capacities. This conceptual framework aligns with the concept of allostasis, which is defined as the set of processes that maintain internal stability in the face of environmental variations. The repeated activation of these adaptive mechanisms generates an allostatic load, which corresponds to the biological cost of chronic adaptation.

Allostatic load has been associated with multisystemic physiological changes (particularly immune, neuroendocrine, and metabolic changes), as well as a subjective state of exhaustion often described as a feeling of overall weariness (Juster et al., 2010). In the operational context, chronic stress is commonly attributable to an imbalance between elevated levels of professional demands and employees' limited personal resources, which can result in a state of exhaustion, wear and tear, a negative attitude toward one's work, and diminished professional efficacy (Hogan et al., 2023).

To reduce fatigue upon returning from missions, a nonpharmacological method selected for resource restoration was L-tyrosine. L-tyrosine, a nonessential amino acid that is capable of being synthesized in the human body, is a precursor to catecholamines, which include dopamine, norepinephrine, and epinephrine. In situations of heightened stress, there is an increase in the consumption of L-tyrosine, which serves to meet the body's increased demand for norepinephrine (through sympathetic activation) and epinephrine (secondary to the production of stress hormones). This consumption has been demonstrated to result in a decrease in tyrosinemia, defined as the amount of tyrosine measured in the blood, during periods of acute stress. Indeed, during periods of stress, there is an increase in the mRNA activity of tyrosine hydroxylase (the rate-limiting step) in the adrenal medulla and in noradrenergic circuits. This increase leads to an increase in the conversion of tyrosine into catecholamines and promotes a metabolic "sink" for tyrosine (Smith et al., 1991; McMahon et al., 1992; Nankova et al., 1999). During periods of heightened cognitive demands and stress, an increase in the activity of noradrenergic neurons is observed. This phenomenon has been shown to result in the "depletion" of tyrosine, which may in turn selectively limit dopamine release by dopaminergic neurons. This dynamic has the potential to contribute to an impairment of the dopaminergic functions involved in motivation and behavioral engagement (Le Masurier et al., 2014). Consequently, in situations involving stress, L-tyrosine—a precursor of catecholamines—is directed primarily toward adrenergic and noradrenergic pathways, resulting in a reduction in dopaminergic synthesis.

The hypothesis of this study was that the supplemental intake of L-tyrosine upon return from a mission could promote the restoration of dopaminergic function in military personnel exposed to prolonged operational stress. Consequently, increasing the availability of L-tyrosine is believed to promote dopamine resynthesis and restore associated functions. It has been demonstrated that dopamine functions not solely as a mediator of pleasure; it also encodes expected value, modulates the effort to

be expanded, influences mood, and supports executive functions (Phillips et al., 2007; Aarts et al., 2011; Salamone et al., 2016; Michely et al., 2020).

The objective of this study was (i) to ascertain whether the concepts of exhaustion and wear-and-tear—often used interchangeably under the term "fatigue" to describe the consequences of chronic stress—correspond to different psychophysiological realities and (ii) to propose a nonpharmacological method for restoring resources upon return from a mission.

Distinguishing between the "wear-and-tear" component and the "exhaustion" component of fatigue is a key challenge, and a better understanding of these processes would not only make it possible to refine the criteria for personnel selection and training but also to develop targeted interventions aimed at strengthening resilience and limiting the cumulative effects of chronic stress over the course of an operational career.

Materials and methods

A statement to confirm that all methods were carried out in accordance with relevant guidelines and regulations.. It was approved by the CPP OUEST II – ANGERS Ethics Committee in France, which is registered with the French Department of Health and Human Services (Clinical Trials.gov ID: NCT04549194; Date of registration: 09/09/2020; <https://clinicaltrials.gov/study/NCT04549194>). All volunteers provided written informed consent before participation.

We followed a cohort of 116 militaries from a French transport facility. The personnel in question were all service members who were fit for deployment overseas and who held deployable positions. The participants were divided into two groups: the deployed group (DG), which was deployed over a 4-month period between 2020 and 2021 in the desert ((Mali, Operation Barkhane), and the nondeployed group (NDG), which remained at the regiment's rear base during this period and served as the control group. Upon returning from the mission, the DG and NDG groups were separated into two subgroups (in a double-blind design): one subgroup received a placebo for one month, and the other received L-tyrosine for one month.

Study treatments (placebo and L-tyrosine) were randomized. The randomization list was prepared by the sponsor's statistician and then transmitted to the pharmacist in charge of conditioning the treatment units. A number was assigned to each subject (subject 01, 02, 03, etc.), and randomization determined allocation to the tyrosine or placebo group. Each subject received one container holding all capsules (tyrosine or placebo) needed for the one-month treatment, i.e. 120 capsules per subject (2 in the morning and 2 in the evening for one month). The treatment units (tyrosine capsules and placebo capsules) were packaged and labeled by the head of the pharmacy department at the military teaching hospital in Toulon, France. The containers were sent to the IRBA pharmacist, together with a sealed envelope containing the randomization order, to allow unblinding if necessary. To conduct a longitudinal follow-up of the four groups, four visits were carried out: prior to mission departure: V1; immediately upon return from mission: V2; one month after returning from mission: V3; and three months after

returning from mission V4. For the DG group, the experimental session upon return from the mission took place less than 24 hours after their return from Mali. All visits took place in the presence of the investigator physician in a medical facility in France.

At each visit, the volunteers completed the questionnaire and performed a blood test. The blood test was aimed at measuring amino acid and BDNF levels. Brain-derived neurotrophic factor (BDNF) was chosen because it is a reliable, multifunctional marker of brain plasticity (Murray et al., 2024). It acts as a structural regulator of synapses, facilitates learning, mediates cognitive effects, and is a candidate biomarker for chronic stress (Herhaus et al., 2024).

Amino acids were measured according to the following procedure: sample preparation followed the Kairos Amino Acid Kit guidelines from Waters. Briefly, 50 μ L of water and 50 μ L of labeled internal standard mixture ($n = 20$) in sulfosalicylic acid were added to 50 μ L of plasma. After protein precipitation, derivatization was performed with the "AccQ. Tag" reagent. The LC–MS/MS method was developed to quantify 45 amino acids in 19 min on a LC40 Nexera (Shimadzu) coupled to a 4000 QTrap (Sciex). The data matrix with the relative area was processed via Workflow4Metabolomics (PLS-DA and correlation) and MetaboAnalyst 5.0 (quantitative enrichment analysis).

BDNF plasma levels were measured via a bead-based immunoassay (Merck® Human Magnetic Bead Panel HMYOMAG-56K) according to the manufacturer's instructions on a Magpix analyzer. The BDNF levels are reported in pg/mL. Amino acids were quantified via high-performance liquid chromatography.

To assess the concepts of wear-and-tear and exhaustion, we used a questionnaire: the Burnout Assessment Tool (BAT). This questionnaire allowed us to measure two subscores: "exhaustion" and "mental distancing" (= unwillingness to invest energy, wear-and-tear) (Schaufeli et al., 2020).

The analysis of the results was conducted by employing nonparametric statistical tests (correlations of Spearman and Friedman ANOVA).

Results

Burn-out assessment tool

For the sake of simplicity and clarity, the present study focuses exclusively on subscores of "exhaustion" and/or "wear-and-tear" (=mental distancing) within the proposed framework (Figure 1). With respect to NDG, we observed no effect of the moment of the visit on either exhaustion (Friedman test, χ^2 (3, $N=24$) = 6.97, $p=0.07$) or wear and tear (Friedman test, χ^2 (3, $N=24$) = 3.27, $p=0.29$). For the DG, we observed no effect of the time of visit on either exhaustion (Friedman test, χ^2 (3, $N=43$) = 1.63, $p=0.65$) or wear and tear (Friedman test, χ^2 (3, $N=43$) = 5.87, $p=0.12$).

Despite these overall results and given the shape of the graphs, we focused on V2 and V3, as these were the periods during which volunteers received the placebo or L-tyrosine (Figure 2).

The exhaustion score decreased in both groups (DG and NDG) that received L-tyrosine (a Wilcoxon matched-pairs test revealed a trend difference between the paired conditions, $T=51$, $Z=1.77$, $p=0.07$ for the DG and $T=10$, $Z=1.78$, $p=0.07$ for the NDG). The variation in the exhaustion score was not significant in either group that received placebo ($p=0.63$ for the DG and $p=0.11$ for the NDG).

The variation in the wear-and-tear score was not influenced by L-tyrosine intake (DG-placebo $p=0.20$; DG-L-tyrosine: $p=0.98$; NDG-placebo: $p=0.73$; NDG-L-tyrosine: $p=0.55$).

Wear-and-tear, exhaustion, tyrosinemia, and tryptophanemia

Analysis of the scores for wear-and-tear, exhaustion, tyrosinemia, and tryptophanemia revealed a negative correlation, in the OPEX group upon return from the mission, between tryptophanemia and wear-and-tear (Spearman $\rho = -0.37$; $p<0.01$).

Blood BDNF Scores

In the DG (Figure 3), a global effect was found overall (Friedman test, $\chi^2(3, N=42) = 21.80$, $p<0.0001$): BDNF decreased after deployment (difference between V1 and V2; Friedman test, $\chi^2(1, N=42) = 16.10$, $p<0.01$) and increased three months after return (difference between V2 and V4; Friedman test, $\chi^2(1, N=42) = 6.10$, $p<0.05$).

In the NDG group, no effect on BDNF was found (Friedman test, $\chi^2(3, N=29) = 5.90$, $p=0.12$).

When we looked more closely at the placebo and tyrosine groups, statistical analysis revealed that in the DG, the increase in BDNF after three months was explained mainly by the group receiving L-tyrosine ($\chi^2(1, N=22) = 4.54$, $p<0.05$; DG placebo: $\chi^2(1, N=20) = 1.80$, $p=0.17$).

Discussion

The study was a double-blind, placebo-controlled trial using a combined psychometric and biomarker approach in an operationally deployed cohort. The aims were i) to determine whether exhaustion and wear and tear share the same consequences of chronic stress or whether they involve different pathways and ii) to determine whether L-tyrosine could promote recovery from chronic stress. Our study of military personnel deployed overseas and those stationed in rear areas revealed that L-tyrosine supplementation may help reduce the exhaustion component of operational fatigue and that wearing-and-tears was negatively correlated with tryptophan levels. We followed a cohort of military personnel on a mission because deployment is a clearly identified situation of chronic stress (Wisén et al., 2023). Other work environments (health care, education, law enforcement, firefighters, traffic controllers, etc.) known for their high stress levels could have been considered (i.e. Catapano et al., 2023; Teixeira et al., 2022; Zeier et al., 1996). Tracking this cohort of military personnel provided a consistent framework in terms of time, location, and conditions of exposure in daily life and during training.

Tryptophan and wear-and-tear

On the other hand, wear and tear were negatively correlated with tryptophan levels. Tryptophan is the precursor of serotonin, a critical neurotransmitter in the regulation of emotional behavior. Chronic stress has been shown to affect serotonin neurotransmission through three main mechanisms: the overexpression of the serotonin transporter (SERT), leading to an increase in serotonin reuptake (Zhang et al., 2012); the functional desensitization of 5-HT_{1A} somatodendritic autoreceptors, resulting in a decrease in the spiking activity of dorsal raphe nucleus serotonin projection neurons and the desensitization of 5-HT_{1A} receptors (Sowa et al., 2018); and the accelerated degradation of serotonin in the frontal cortex, the striatum and the hippocampus, as reflected by an increased 5-HIAA/5-HT ratio (Ahmad et al., 2010).

Chronic stress does not reduce available serotonin; it profoundly disrupts the inhibitory mechanisms that regulate its release and throws the amygdala–prefrontal cortex circuit—which governs emotional control—out of balance (Laaris et al., 1995 Liu et al., 2020). In humans, low availability of SERT in the dorsal raphe nucleus is associated with increased reactivity of the medial amygdala to frightening faces and enhanced connectivity between the amygdala and the dorsolateral prefrontal cortex. These findings demonstrate that serotonergic signaling directly modulates this circuit (Janet et al., 2023).

This serotonergic deficit is one of the central mechanisms linking chronic stress and depression. Chronic stress does not merely “deplete” cerebral serotonin; rather, it alters the inhibitory mechanisms governing its release and concurrently perturbs the functional balance between the amygdala and prefrontal cortex. This combined disruption contributes to impaired emotional regulation, characterized by heightened affective reactivity and reduced top-down executive control. Our results are consistent with the notion of “depletion” of serotonin indirectly highlighted by the level of tryptophan (its precursor). Indeed, we recently suggested that the 'wear and tear' component of operational fatigue could be linked to emotional overload (Ramdani & Kotsou, 2025). The observed associations between tryptophanemia and the wear-and-tear scores do not allow us to infer the direction of causality. A reduction in serotonin availability could contribute to the development of wear-and-tears, with the latter reflecting a state of emotional dysregulation. Conversely, sustained emotional overload may enhance serotonin turnover, accelerate its depletion, and thereby manifest as wear-and-tears. In one scenario, emotional overload emerges as a consequence of serotonin depletion; in the other, it constitutes a causal factor of this depletion. These mechanisms are not mutually exclusive and may coexist or reinforce one another.

L-Tyrosine and Exhaustion

Although the two-sided test did not reach statistical significance ($p = 0.07$), this effect was significant in the one-sided analysis. A one-sided test was justified *a priori* on the basis of a strong directional hypothesis regarding the expected effect of L-tyrosine on operational fatigue. Previous studies have reported that L-tyrosine can improve sleep in certain forms of depression (Mouret et al., 1988). Accordingly, the observed reduction in exhaustion may have been mediated, at least in part, by improved sleep quality.

In contrast, L-tyrosine did not appear to improve the wear-and-tear component of operational fatigue.

BDNF and catecholamines

Brain-derived neurotrophic factor (BDNF) has a neurotrophic function connected to various physiological functions in the brain, including neuroplasticity and sleep (Schmitt et al., 2016). As BDNF is a potential marker of chronic stress, a decrease in BDNF in the DG was expected (Herhaus et al., 2024). An increase in BDNF after the three-month recovery period was anticipated, as exposure to deployment-related stressors had terminated. However, it was puzzling at first that BDNF increased only in the deployed group that received L-tyrosine. Given our hypothesis that L-tyrosine would restore dopaminergic pathways, this finding is reasonable since dopaminergic activity is one of the main positive regulators of BDNF (brain-derived neurotrophic factor) expression in several brain regions *via* well-identified molecular mechanisms. Dopamine activates BDNF synthesis via at least three parallel pathways (D1/cAMP/CREB, D1-D2/Ca²⁺/CaMKII, D2/PP1/nuclear CaMKII δ 3) (Zhao et al., 2013; Hasbi et al., 2011; Shioda et al., 2015), with marked regional and cellular specificities, forming a reciprocal regulatory loop since BDNF itself in turn regulates the expression of D1 (Do et al., 2007) and D3 (Sokoloff et al., 2002) dopamine receptors. However, norepinephrine is the most potent monoaminergic inducer of BDNF synthesis, eliciting approximately twice the effect of dopamine at a substantially lower concentration (1 μ M vs. 150 μ M). This enhanced efficacy is mediated by a distinctive synergistic interaction between the α 1-PKC and β 1/ β 2-cAMP signaling pathways, underscoring the superior molecular efficiency of NE (Juric et al., 2006). In contrast, dopamine induces BDNF expression in cortical astrocytes predominantly via cross-talk with β -adrenergic receptors rather than through direct activation of their canonical D1/D2 receptors (Koppel et al., 2018), with only a minor contribution from α 1-adrenergic and dopaminergic receptors. L-tyrosine supplementation not only supported dopaminergic signaling but also broadly enhanced catecholaminergic pathways and contributed to increased BDNF production.

Furthermore, BDNF plays a fundamental role in regulating sleep by acting at several levels: sleep architecture, circadian rhythm, and homeostasis (the mechanism of recovery following sleep deprivation). BDNF improves sleep by stabilizing REM sleep via the brainstem, deepening NREM sleep via slow waves, and synchronizing the circadian clock via the NSC—three complementary mechanisms that make BDNF a central regulator of sleep architecture (Schmitt et al., 2016; Garner et al., 2018; Liang et al., 2000). Our results revealed that the “exhaustion” component of operation was improved in DGs receiving L-tyrosine. We suggest that the beneficial effect of L-tyrosine on exhaustion could be mediated by the increase in BDNF induced by the increased catecholaminergic activity generated by L-tyrosine supplementation. An increase in BDNF promotes a better quality of sleep and explains the influence of L-tyrosine on sleep in certain forms of depression (Mouret et al., 1998). Previous studies have shown that sleep deprivation leads to a significant reduction in plasma BDNF levels, suggesting a homeostatic regulatory mechanism designed to protect the cortex from excessive excitation (Kühn et al., 2016), leading to a potentially vicious cycle of exhaustion.

Nonetheless, in situations of depression, the influence of serotonin cannot be overlooked. Indeed, serotonin is a well-documented activator of BDNF synthesis, with distinct mechanisms depending on the cell type and brain region involved (Juric et al., 2006). There is also a bidirectional and mutually

reinforcing relationship between serotonin and BDNF (Mattson et al., 2004). This coregulatory loop makes serotonin and BDNF two deeply interdependent systems involved in neuronal plasticity, stress resilience, and the pathophysiology of depression (Leschik et al., 2022). Given the relationship between tryptophanemia and the wear-and-tear score, one can assume that tryptophane supplementation might have fostered an increase in BDNF, on the one hand, and promoted the recovery of wear-and-tears, and, on the other hand, increased BDNF.

BDNF, adrenaline, and serotonin form a network of mutual regulation at the heart of neuroplasticity and mood disorders, which explains why their joint dysregulation is observed in depression, chronic stress, and various neuropsychiatric disorders (Popova & Naumenko, 2019). In our framework, exhaustion and wear-and-tear and two aspects of operational fatigue involve two neurobiological pathways (catecholaminergic and serotonergic), and BDNF is a hub in the network of dysregulation promoted by exposure to chronic stress. Exhaustion and wear-and-tear are clinical presentations, and a decrease in BDNF could both be the cause and consequence of these symptoms, considering its mutual regulation with amines, which is one of the most important aspects of brain neuroplasticity (Alsalloum et al., 2026).

Conclusion

In our proposal, both wear and tear and exhaustion are consequences of chronic stress. However, exhaustion refers to overload involving catecholaminergic pathways and dopaminergic depletion, resulting in a decrease in BDNF, affecting sleep quality and contributing to exhaustion. Poor sleep quality could contribute to a decrease in BDNF and promote a vicious cycle of exhaustion.

Wear-and-tear refers to emotional overload involving the serotonergic pathway without prejudging whether serotonin causes emotional disorders or whether emotional disorders cause serotonergic disorders.

L-Tyrosine seems to reduce exhaustion by fostering catecholaminergic pathways and enhancing BDNF synthesis, promoting better sleep.

Distinguishing between exhaustion and wear-and-tear would generally lead to better treatment of burnout and to better understanding responses—or a lack thereof—to various therapeutic approaches. Furthermore, this could pave the way for targeted methods to prevent the harmful effects of chronic stress by promoting individual sleep to prevent exhaustion and using an organizational psychology approach to prevent wear-and-tear.

Declarations

Authorship Each author have made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; have drafted the work or substantively revised it: LN : acquisition, analysis, interpretation of data and drafted work; AS-CL-CL-CD: analysis, interpretation of

data and drafted work; GE-GM: major contribution to the acquisition of data CR : conception, acquisition, interpretation of data and drafted work.

Data availability statement Our data cannot be shared openly, to protect study participant privacy, because of their work and for their own safety

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

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The authors declare no conflict of interest.

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Figures

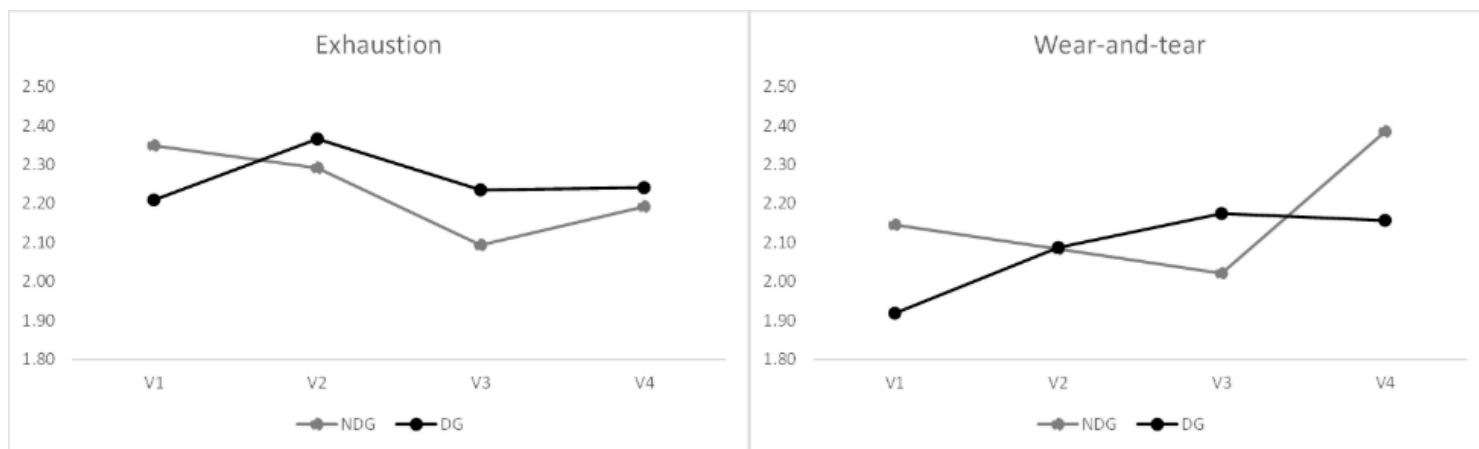


Figure 1

On the left, the score for the “exhaustion” subscale; on the right, the score for the “wear-and-tear” subscale; on the black: the deployed group (DG), in gray: the nondeployed group (NDG)

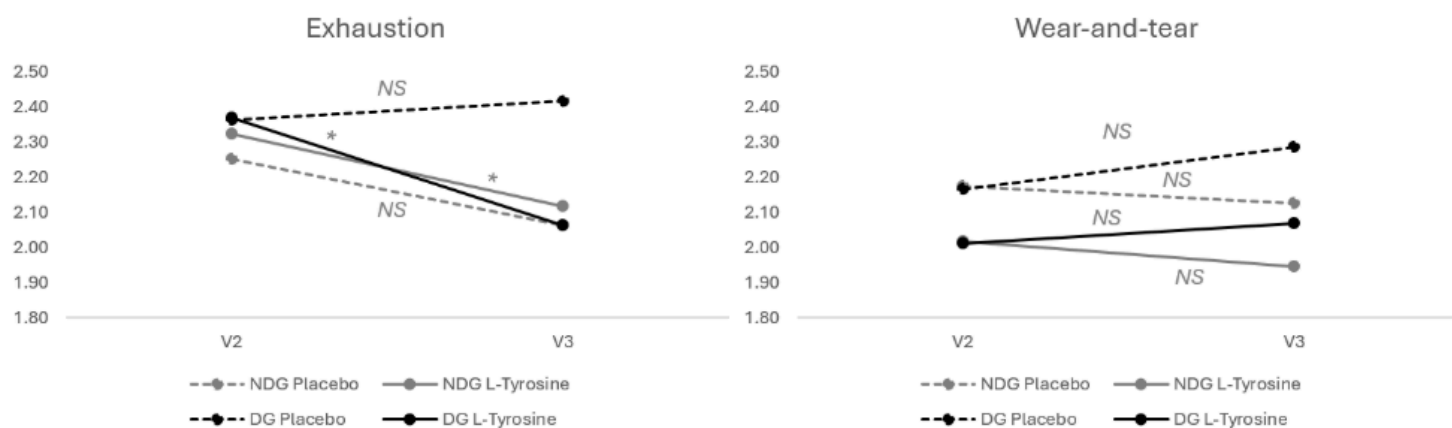


Figure 2

On the left, the score for the “exhaustion” subscale; on the right, the score for the “wear-and-tear” subscale; on the black side, the deployed group (DG); on the gray side, the nondeployed group (NDG); on the solid line, the group that received L-tyrosine; on the dotted lines, the group that received placebo; NS, nonsignificant; * $p < 0.05$ unilateral Wilcoxon match pair tests

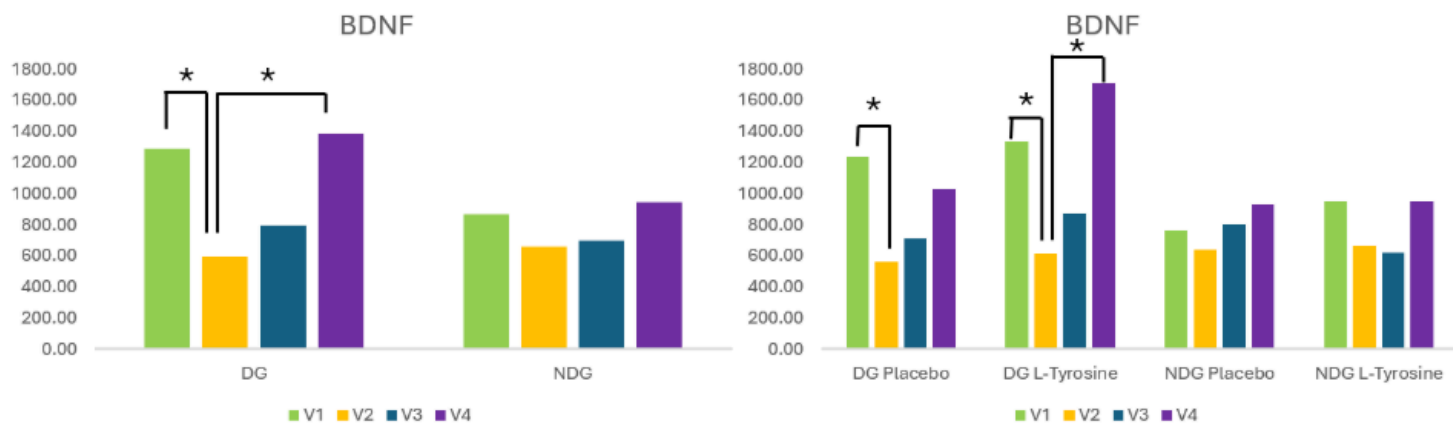


Figure 3

Blood BDNF score DG: deployed group; NDG: nondeployed group. In green, before deployment; in yellow, just after return; in blue, one month after return; in purple, three months after return; * $p < 0.05$