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PERSPECTIVE PAPER

IN BETWEEN THE PSYCHOLOGICAL AND PHYSIOLOGICAL SELF – THE IMPACT OF COVID-19 PANDEMIC ON THE NEURO-SOCIO-ECOLOGICAL AND INFLAMMATORY MIND-BODY-BRAIN SYSTEM

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Abstract

The COVID-19 pandemic has had a profound impact on individuals' sense of self perturbating the sense of connectedness with the others, touching upon deep existential fears and deep intersubjective and cultural layers, emphasizing the importance of a neuro-socio-ecological alignment for the sense of security of psychological self. We can still observe after years how social distancing measures, quarantines, and lockdowns have disrupted social connections and routines, leading to feelings of isolation, anxiety and depressive symptomatology. Furthermore, from a physiological perspective, some people continue to experience health problems long after having COVID-19, and these ongoing health problems are sometimes called post-COVID-19 syndrome or post-COVID conditions (PASC). In this complex scenario, through the operationalization of the sense of self and its psychological and physiological baseline, our aim is to try to shed some new light on elements of resilience vs. vulnerability. Here we intend the self and its baseline as the crossroads between psychology and physiology and we show how COVID-19 pandemic, especially in post-COVID-19 syndrome (PACS), left traces in the mind-body-brain system at a neuro-socio-ecological and inflammatory level.

Key words: self, psychological, physiological baseline, post-COVID-19 syndrome-PACS, neuro-socio-ecological inflammatory markers

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Introduction

The COVID-19 pandemic has affected our sense of self and our relatedness with others, as well as our psychological and physiological well-being encompassing several manifestations of symptoms in the body-brain-mind system. From a psychological perspective, in particular recent studies have shown that the COVID-19 pandemic crisis has touched upon our existential fears (Scalabrini, Mucci, Angeletti, et al., 2020) and affected our sense of self and self-other relationship (Scalabrini, Xu, et al., 2021). Moreover, the pandemic crisis was mostly perceived as a threat to physical and psychological sense of safety leading to especially feelings of depression and ruminative thought modes (Benedetti et al., 2022; Liu et al., 2022; Mazza et al., 2021).

While, on a psychobiological level, it has been shown that COVID-19 induced systemic inflammation in the whole body, including the brain, and leading to severe neuropsychiatric manifestation over the years (Mazza et al., 2021; Nalbandian et al., 2023; Nalbandian et al., 2021)

These consequences of the COVID-19 pandemic revealed, from one side, the importance of our basic psychological needs, including relatedness, autonomy and agency as well as our relation with the environment (Han et al., 2023; Šakan et al., 2020). On the other side Sars-Cov-2 infection exerted a detrimental impact on mental illness, possibly sharing pathogenetic mechanisms with depressive disorders, through immune-mediated mechanisms that disrupt the physiological brain-body crosstalk (Branchi et al., 2021).

In this complex scenario the perspective of the concept of self and psychological and physiological

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baseline might contribute to having a multifaceted model that comprises neuro-social-ecological and psychological components (Scalabrini, Xu, et al., 2021) together with more psychobiological and inflammatory elements (Mazza, Palladini, Poletti, et al., 2022).

Our aim is to unravel how the two different, but inter-related psychological and physiological components might find their crossroads in the light of the consequences related to the COVID-19 pandemic.

Psychological and neuro-socio-ecological features related with COVID-19 pandemic

The self and its psychological baseline

We can consider the self as the fundamental core of our mental life and well-being. Our self allows for internal cognition like mind-wandering (Christoff et al., 2016; Scalabrini, Schimmenti, et al., 2022; Smallwood et al., 2021) and mental time travel (Northoff, 2017; Schacter et al., 2012). The self is also related to the external environment through the sense of agency (Ebisch & Aleman, 2016) and its social relationship with others (Guisinger & Blatt, 1994; Luyten & Blatt, 2013) in terms of connectedness (Carhart-Harris et al., 2018; Mucci, 2018b, 2022) or empathy (Di Plinio et al., 2022; Ebisch et al., 2022; Gallese, 2003). Thus, the self can be considered an interface between internal and external stimuli.

Moreover, the self is also intrinsically related to the body: for instance, the group around Tallon-Baudry demonstrated how our psychological sense of self is based on body–brain coupling by temporal synchronization of interoceptive stimuli from the heart and stomach with the brain's spontaneous activity in the insula, the anterior midline regions and visual cortex (Park et al., 2014; Park & Tallon-Baudry, 2014). Given its role in relation to the body (e.g., interoception), internal and external cognition, the self, modulated by the spontaneous activity of the brain (Northoff & Huang, 2017), has been characterized as an integrative function (Sui & Humphreys, 2015) that provides an internal-external relation and thereby serves as a "psychological baseline" (Northoff, 2016; Scalabrini, Mucci, Esposito, et al., 2020; Scalabrini, Mucci, et al., 2022; Scalabrini, Schimmenti, et al., 2022; Scalabrini, Xu, et al., 2021).

The etiopathogenesis of a resilient vs. a vulnerable self

Intriguingly the development of the self finds its priors in early internal-external relational experiences with primary caregivers in the context of attachment. Thus it has been proposed that our personal experience of ourselves and its connection with the body, others and the environment might be dependent on the encounter with the other and his/her capacity to attune/regulate/synchronize with the infant (Mucci, 2018b; Mucci & Scalabrini, 2021; Schore, 2021; Trevarthen & Aitken, 2001). Indeed, bio-behavioral synchrony is an important aspect of mother–infant attachment (Feldman, 2007), that contributes to the formation of the sense of self and relatedness (Mucci & Scalabrini, 2021; Scalabrini et al., 2018; Scalabrini, Mucci, et al., 2022). Through synchronization the mother regulates the infant's temperature (Levin, 2006), heart rate (Feldman et al., 2011), sleep and arousal (Feldman et al., 2002). Mothers, moreover, also regulate their infants' immune function by breastfeeding, synchronizing their gut microbiota and antigen-specific antibodies (Arrieta et al., 2014).

Together, these observations about the early mother-infant relation strongly speak for a key role of the relation with the significant others (e.g., the caregiver) and their capacity of regulation/attunement/synchronization in constituting the self as an internal-external relation interface in later adulthood. In summary, we can speak of the degree of connectedness between the caregiver and the child that constitute the building blocks of the developing self in relation to the world and its characteristic of resiliency vs. vulnerability in dealing with stressful and uncertain moments of life.

The development of self and its degree of connectedness seems very close to the broader concept of connectedness developed by Porges in describing the connection to the body (Porges & Phillips, 2014), to others, and the world in general (Carhart-Harris et al., 2018; Watts et al., 2022). Recently in dynamic psychology and psychoanalysis, Mucci (Mucci, 2018a, 2018b, 2022) proposes the construct of connectedness as fundamental in the social exchanges of human beings and in maintaining a bond to life and is itself a form of resilience against adverse life traumatic experiences that might disrupt our sense of self and relatedness with others. Resiliency here refers, in the intersection between psychology and biology, to what Mucci defines as the human ability to resist adversities and/or to respond to trauma of various intensities (Mucci, 2018a, 2018b, 2022). On this regard, lately Scalabrini, Mucci and Northoff proposed a nested hierarchy of self and its trauma (Scalabrini, Mucci, et al., 2022) suggesting how different levels of traumatic experiences might have and enduring effect in yielding a trauma-based topographic and dynamci re-organization of the nested model of the self (Qin et al., 2020; Scalabrini et al., 2018; Scalabrini, Wolman, et al., 2021)

The psychological baseline and its neuronal activity

Overall, the concept of psychological baseline refers to the idea that there is a fundamental level of neural activity that underlies all cognitive and emotional processes, i.e., a "default mode" of neural activity that is present even when an individual is not engaged in any specific task or cognitive process. This default mode is thought to represent the basic level of neural activity that supports self-referential processing, attentional control, and other fundamental aspects of cognition (Northoff, 2016; Northoff et al., 2022; Scalabrini, Schimmenti, et al., 2022).

According to Northoff and Scalabrini (Northoff & Scalabrini, 2021; Northoff et al., 2022), disruptions to this psychological baseline can lead to a range of psychological disorders, including depression, anxiety, and schizophrenia. They argue that these disorders are characterized by a disturbance in the normal functioning of the default mode functionality of the brain (Raichle, 2009, 2015a, 2015b), which leads to abnormal patterns of neural activity.

One implication of the concept of psychological baseline is that it suggests that there may be a fundamental level of neural activity that is shared across all individuals, beyond or beneath the surface of their specific cognitive or emotional perceived states. This implies that the respective concept of psychological baseline might provide a useful framework for understanding the relationship between neural activity and subjective experience. By studying

the fundamental level of neural activity that underlies all cognitive and emotional processes, researchers can gain insight into the neural and psychological basis of disorders or impairments that were exacerbated by the COVID-19 crisis.

In sum, the construct of self and psychological baseline, here considered as the degree of connectedness between our body, environment and mind, serves as a reference for subsequent cognition, affect, and other functions and it seems intrinsically related to the spontaneous activity of the brain, i.e. the physiological baseline (Scalabrini et al., 2023). Thus the construct of self and its baseline, together with its characteristic of vulnerability and resiliency, can be considered the point where the psychological and the physiological become interlocked and share similar dynamics and functions (Northoff & Scalabrini, 2021) as their "common currency" (Northoff et al., 2020a, 2020b).

The impact of the COVID-19 pandemic on the psychological self

The COVID-19 pandemic has had a profound impact on individuals' sense of self perturbating the profound sense of connectedness with the others touching upon deep existential fears (Scalabrini, Mucci, Angeletti, et al., 2020) and deep intersubjective and cultural layers emphasizing the importance of a neuro-socio-ecological alignment for the sense of security of psychological self (Scalabrini, Xu, et al., 2021). We can still observe how social distancing measures, quarantines, and lockdowns have disrupted social connections and routines, leading to feelings of isolation, anxiety. According to a systematic review and meta-analysis, COVID-19 can involve persistent psychiatric sequelae, and other medical complications that last weeks to months after initial recovery (Lopez-Leon et al., 2021; Zeng et al., 2023)

Some people continue to experience health problems long after having COVID-19, and these ongoing health problems are sometimes called post-COVID-19 syndrome or post-COVID conditions (PASC, e.g., (Nalbandian et al., 2021).

Additionally, the pandemic has highlighted existing social and economic disparities, with marginalized communities experiencing greater health and financial consequences (Bambra et al., 2020). In response to these challenges, manifestations of vulnerability and resiliency have been seen and many individuals have had to reimagine their sense of self and adapt to new circumstances. From our perspective our sense of self and psychological baseline could serve as a resilient factor but, at the same time, has been the most threatened for our well-being. We hypothesize that the perception of connectedness with self, body, others and environment revealed the self's adaptive and maladaptive features and, because of that, was modified by the threatening events related to COVID-19 pandemic manifesting its internal vulnerability (e.g., psychological difficulties).

To put it simply, our idea is that our self and our degree of connectedness with the body, others and the environment could be the factor more threatened by an external event like the COVID-19 pandemic and, at the same time, the factor more associated with resiliency and coping during such times. Thus, the self and its sense of connectedness might have a central role associated with mental health issues during times of threat, like the covid-19 outbreak (Scalabrini et al., 2023).

This suggests a fundamental role for the self as considered an internal-external interface serving as an adaptive factor suggesting how promoting psychological and social well-being should target the experience of connectedness/attunement/synchrony as a key factor to better develop coping and resiliency features.

Thus, our self and its "psychological baseline" it is what has been mostly destabilized by the COVID-19 pandemic leading to clinical and subclinical behavioral and psychological symptoms comprising COVID-related fear experience (Schimmenti et al., 2020), higher degree of emotion dysregulation (Siegel et al., 2021) and rumination (Benedetti et al., 2022; Satici et al., 2022). Moreover, we hypothesize that people selves characterized by a lower degree of connectedness are those subjects who still report psychopathological or psychiatric difficulties after three years of COVID-19 when compared to those subjects that showed more resilient capacities.

Physiological and psychobiological sequelae of COVID-19

The neuropsychiatric face of COVID-19: a murky issue

Three years after the beginning of COVID-19 outbreak, the so-called post-acute COVID-19 syndrome (PACS, (Nalbandian et al., 2023; Nalbandian et al., 2021) is emerging as a major challenge of our epoch. Up-to-date systematic reviews suggest millions of people worldwide struggle with delayed complications of Sars-CoV-2, impairing their everyday functioning and posing an add-on burden on the hill of the pandemic itself. The varied and relapsing symptoms entail dyspnea, hypoxia, joint muscle and pain, paresthesia, dysgeusia, fatigue, insomnia, anxiety, and cognitive dysfunction both at subjective and objective level, altogether indicating the whole body retains record of the original illness insult.

Most strikingly, the phenomenon termed 'happy hypoxemia' represents to date a hot topic in literature focusing on PACS. Under this heading exists COVID-19 survivors in whom low saturation levels do not couple with subjective dyspnea, raising questions about pathophysiological drivers of such a paradox (Dhont et al., 2020).

Among the wide spectrum of organic, neurological, and psychopathological sequelae of the infection, the impressive rate of psychiatric outcomes in the sub-acute stages substantially exceeds the pre-pandemic epidemiology (Mazza, Palladini, Poletti, et al., 2022; Mazza, Palladini, Villa, et al., 2022; Vai et al., 2021). Approximately 50% of survivors experience clinically significant forms of psychopathological suffering, with depression and cognitive difficulties persisting also in the long run (Mazza, Palladini, De Lorenzo, et al., 2022). Even more alarming, recent meta-analysis dealing with the longitudinal course of such conditions reveal that estimates progressively increase, which may indicate that these symptoms are more likely to develop than persist post-infection (Premraj et al., 2022), or that patients overcome stigma and finally present their symptoms to the physicians.

In this regard, depressive symptomatology figures prominently in the aftermath of COVID-19, adding strain on the healthcare system due to its unique persistence and disabling impact. Its phenotypes widely resemble the Major Depression Disorder's (MDD) clinical pattern, sharing a wide range of psychopathological, cognitive, and organic implications, as well as

neurobiological underpinnings. Low mood associates with impaired neuropsychological functioning, leading COVID-19 survivors to experience cognitive deficits in visuospatial abilities, executive functions, and verbal fluency (Poletti et al., 2021). Among psychopathological issues linked to the infection-triggered depressive syndrome, fatigue has been consistently reported as one of the leading complaints among COVID-19 patients. Fatigue within depressive psychopathology's frame concerns subjective physical exhaustion (Ortelli et al., 2021), slowed thinking and decreased motivation and initiative (Mattioli et al., 2021; Ortelli et al., 2021). In the framework of COVID-19 pandemic, evidence exists indicating depression in the sub-acute stages as a major driver of long-lasting post-viral fatigue (Mazza, Palladini, De Lorenzo, et al., 2022). Further, novel insights reveal that mood-congruent cognitive distortions represent a core feature of post-acute depressive psychopathology, showing overlapping structure of associations with both negative thinking styles and severity of self-rated depression when compared to a cohort of MDD patients (Benedetti et al., 2022).

According to the foregoing, also the clinical and neurobiological features of post-traumatic distress among COVID-19 survivors largely overlap with post-traumatic stress disorder (PTSD) arising from different emergency circumstances (Chamaa et al., 2021). In the context of COVID-19 outbreak, post-traumatic symptoms severity seems to be fostered by irrational survivors' guilt feelings, as usually occurs in the most severe and treatment-resistant forms of PTSD (Wilson et al., 2006). Recently, it has been raised the possibility that PTSD-related hyperarousal and intrusion may worsen survivors' 'brain fog', defined as a general sense of inefficiency in concentrating, decision-making and doing daily activities (Turana et al., 2022).

As for most depressive and anxiety disorders, sex is a major factor influencing incidence and course of PASC, affecting 3:1 females to males (Mazza, Palladini, Villa, et al., 2022). Beyond the ascertained risk factors, encompassing demographics (i.e., sex, high educational level), and clinical history (i.e., precedent diagnosis of psychiatric disorder), forced isolation following the virus clearance has been recognized as one of the leading factors promoting post-COVID psychopathology. Notwithstanding, the interdependence between COVID-19 disease severity and the following neurocognitive implications is still matter of debate, most findings suggest both asymptomatic or mild patients have similar susceptibility to neuropsychiatric outcomes, reinforcing the idea of shared molecular or affective pathways, along with personality features and pre-morbid physiological status may enhance or dampen vulnerability to post-COVID distress. To lend some context to that claim, novel investigations highlight the prominent role of survivor guilt as a root driver for psychopathology in the post-COVID stages, being unaffected by neither familiar experience of illness nor the infection's clinical course (Palladini et al., 2023). Likewise, accumulating evidence supports the notion of dispositional qualities (similar to what we proposed to name as psychological baseline) serving as protective factors against new onset neuropsychiatric conditions, leaving aside the strength of detrimental factors such as isolation and stigma (Xiao et al., 2023).

According to the latest insights, health care services themselves do not adequately respond to the compelling needs of 'long haulers', who are left alone dealing with uncertainty of their symptoms' evolution (Samper-Pardo et al., 2023). The extreme heterogeneity in the PACS symptoms along with the lack of a standard to denote the many phenotypic manifestations may add to the confusion in which already lie both policymakers, patients, and physicians (Deer et al., 2021). Lay media give a clear picture of an increasing social concern about the unmet need for COVID long-haulers, presenting persisting symptoms that puzzle the medical class and are often dismissed as clinically irrelevant, despite their major impact on daily functioning (Mariani, 2022).

Briefly resuming, whilst consensus exists about the urgency of effectively treating neuropsychiatric outcomes of COVID-19, new advances are required to elucidate the endophenotypes of PACS. A promising candidate could be the 'sense of self' and its biological counterpart of baseline neural activity, quite possibly impacted by the COVID-19 insult. We speculate that through the lens of psychological baseline we may deepen our understanding of mechanisms upholding post-COVID-19 psychopathology.

Behind the Neuropsychiatric sequelae: neurobiological drivers

Efforts are underway to depict neurobiological drivers facilitating the emergence of neuropsychiatric conditions. The immune-inflammatory signaling pathway has gained widespread attention as the leading neurobiological mechanism behind PACS. Several investigations support the notion of the immune system going into overdrive, fueling innate immune response, and simultaneously inducing suppression of the adaptive immunity arm, resulting in a persistent inflammatory response strongly implicated in neuropsychiatric features of PACS. A persistent inflammatory status in turn affects Blood Brain Barrier (BBB) permeability, microglia and astroglia activation, oxidative stress, and the HPA, as observed in Mood Disorders (Benedetti et al., 2020).

Weak BBB may expose the brain to molecules and cells involved in peripheral inflammation, triggering neuroinflammatory processes. Prompted microglia and astrocytes switch to their pro-inflammatory phenotypes (i.e., M1 and A1 respectively) with subsequent massive release of pro-inflammatory cytokines such as TNF-a, IL-1β, IL-6, nitric acid, ROS, and glutamate and thus resulting in enhanced excitotoxicity and cytotoxicity. New data confirm that higher baseline inflammatory biomarkers in the periphery are associated with the severity of long-term anxiety and depressive symptoms (Mazza et al., 2020; Mazza et al., 2021). More in-deep investigations identify IL-6 and TNF-α as reliable predictors of post-COVID depression (García et al., 2021).

A second route by which systemic inflammation may give rise to psychiatric manifestations is the cytokine-induced shift in tryptophan metabolism toward kynurenine via indoleamine 2,3-dioxygenase (IDO) induction. This implies the depletion of tryptophan available for serotonin synthesis (Dantzer et al., 2008).

Additionally, pro-inflammatory mediators reaching the brain may engender aberrant release of glutamate by astrocytes and decrease its reuptake, resulting in apoptotic phenomenon. Atypical glutamatergic NMDA-NO signaling in COVID-19 survivors may provoke alterations in limbic regions in the brain cortex, contributing to the development of psychotic, mood, and anxiety-related disorders in the aftermath (van Vuren et al., 2021).

Among the biological mechanisms capable to maintain psychiatric symptomatology, dysregulation of

renin angiotensin system (RAS) has been indicated as the primary trigger of this self-reinforcing cycle. Indeed, Angiotensin Converting Enzyme 2 (ACE-2) serves as receptor for Sars-CoV-2 entry and contextually it plays a major role in the regulation of RAS by enhancing its anti-inflammatory and anti-fibrotic arm. Exposure to the virus implies downregulation of ACE-2, causing offsets towards the ACE/Ang-II branch of the system and facilitating, in turn, its pro-inflammatory activity (Saikarthik et al., 2022).

Recent studies support the role of ACE-2 in determining neuropsychological impairment in survivors, widely recognized as a regular feature of the psychiatric manifestations. Its implication in neuropsychiatric sequelae stems from its crucial role in neurogenesis under homeostatic conditions. It seems that downregulation of this receptor could hinder the release of neurotrophic factors (e.g., CREB, BDNF), hypothesis further strengthened by findings of reduced hippocampal volume in COVID-19 survivors experiencing PTSD and cognitive difficulties (Lu et al., 2020; Tu et al., 2021).

Another possibility to explain neuropsychiatric sequelae arises from the hypothalamus-pituitary-adrenal (HPA) axis dysfunction. When a persistent hyperinflammatory state exists, abnormal levels of cortisol are released due to elevated concentration of immune mediators irrespective of circulating ACTH rates. Resistance of HPA axis to glucocorticoids negative feedback has been largely associated to post-COVID anxiety, depression, and PTSD symptoms. Moreover, a bidirectional causality amplifies the role of HPA axis in Post-COVID psychopathology. In addition to being activated by sustained inflammation, also psychological stressors are known to activate the HPA axis and sympathetic nervous system (SNS) thus, affecting mood through immune modulation in the CNS. From a clinical point of view exposure to early or recent stress is associated with a higher risk of an MDD episode also affecting the brain structure and functional connectivity (Juruena et al., 2018). Altogether, disruption of the immune-neuroendocrine homeostasis following the infection may create a breeding ground for development of psychopathology via structural and functional alterations of the brain.

Evidence from Neuroimaging

The latest findings in the neuroimaging field support the notion of extensive involvement of the brain in the observed post-COVID psychiatric issues. Despite the specific signature of neuropsychiatric symptoms that has yet to be established, alterations in grey matter volumes have been largely documented. In particular, a recent study demonstrates an enlargement of cortical and sub-cortical areas spanning from frontotemporal regions, limbic structures, and basal ganglia in neuropsychiatric Long-COVID syndrome compared to healthy conditions (Besteher et al., 2022). On the contrary, most investigations pinpoint brain atrophy in critical regions for affective regulation go together with psychiatric symptoms' worsening in COVID-19 stages (Benedetti et al., 2021). Interestingly, marked surface deformations were spotted in the basal ganglia and in the thalamus in a group of patients exhibiting long-term fatigue. In the same cohort, significantly higher fractional anisotropy in the thalamus was detected (Heine et al., 2023). For their part, structural connectivity analysis revealed a widespread pattern of white matter deterioration related to cognitive impairment, and depressive and post-traumatic symptoms in survivors (Benedetti et al., 2021; Huang et al., 2023). Even subjective cognitive complaints seem to mirror brain structural abnormalities, with an increased in Radial Diffusivity (RD), Mean Diffusivity (MD) in several tracts of the white matter skeleton (Paolini et al., 2023). When specifically looking at cognitive decline, a large case-control longitudinal study performed on subjects from the UK Biobank before and after COVID-19, found a greater decline of objectively measured cognitive abilities in post-COVID patients associated with new-onset reduced cerebellar volume (Douaud et al., 2022), thus suggesting a causality connection between infection, brain damage, and cognitive impairment. PTSD symptomatology after COVID-19 were found to be associated with reduced volumes of the left hippocampus and amygdala (Tu et al., 2021) and with decreased FA levels (Benedetti et al., 2021).

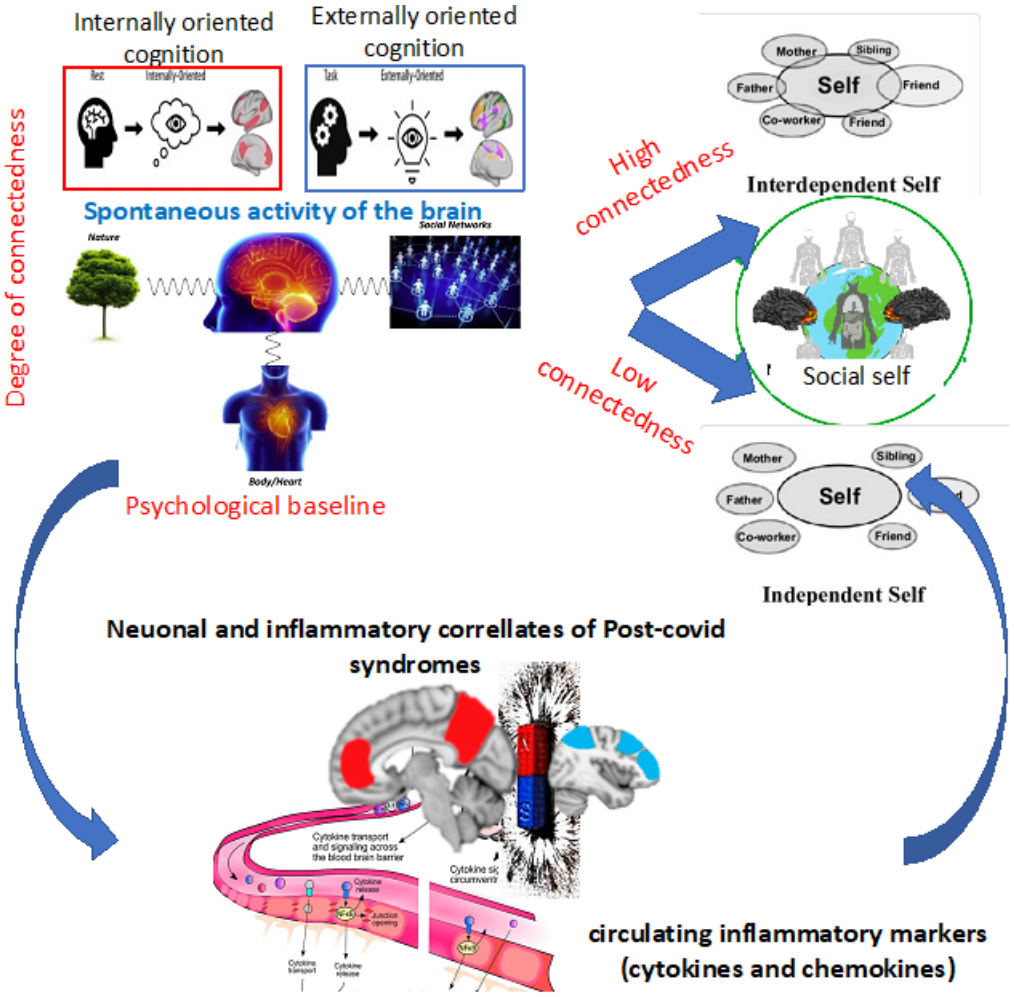
Abnormal resting-state connectivity was also found in COVID-19 patients after the illness resolution, showing altered dynamic functional network connectivity between sensorimotor and visual networks, whose increased occurrence positively correlates with PTSD symptoms' intensity (Fu et al., 2021). Specific alterations in the amplitude of low-frequency fluctuation (ALFF) in correspondence to limbic regions parallel to the worsening of insomnia severity were found even one year after the infection (Du et al., 2022). Moreover, multivariate pattern connectivity analysis (MVPA) applied to resting state data identified in the dorsal cingulate cortex of COVID-19 survivors a crucial region whose connectivity pattern with pre-frontal areas decreases proportionally to PTSD symptoms exacerbation, whereas its functional coupling with areas of the Default Mode Network (DMN) boost as the symptoms worsen. Similar alterations were outlined regarding connectivity between dorsolateral pre-frontal cortex (salience network) and DMN regions according to baseline inflammatory parameters (Benedetti et al., 2021).

To sum up, the above findings support the notion of disruption in the structural and functional connectome as regular brain correlates of PACS neuropsychiatric features.

Conclusions

In conclusion here we propose a perspective that considers how our well-being and our health might be compromised when our psychological baseline is impaired. The quality of our baseline self can be resilient, either vulnerable depending on its etiopathogenesis. Indeed, supporting this hypothesis, recently it has been suggested that psychopathological disorders, as for instance in the case of depression, reflect excessively strong "priors" that render patients insensitive to low-level stimuli or abnormally sensitive to prediction error signals (Pezzulo et al., 2021). This seems to be in line with our data of an abnormal physiological and psychological baseline in depression (Scalabrini, Schimmenti, et al., 2022; Scalabrini, Vai, et al., 2020). Indeed, from the personality-functioning perspective, depressed persons reported poorer interpersonal functioning, and somewhat more prominently, greater self-pathology (Vittengl et al., 2023). Moreover, the state of the art suggests that psychological baseline and the spontaneous activity of the brain are key psycho- and bio-logical markers for targeting human well-being considering psychological, bodily and social

Figure 1. *Visual representation of the proposed integration to further investigate the psychological and physiological self from a neuro-socio-ecological and inflammatory perspective*



health. Moreover, these aspects might have an effect on social connectedness and interdependency (Markus & Kitayama, 1991) increasing human capacity to live in more inclusive society. Is this the case of the effect of the COVID-19 pandemic after years?

As largely known a vulnerable psychological and physiological baseline, in case of a trigger could increase the risk of developing depressive psychopathology. This process is extremely relevant in COVID-19 survivors, where subjects, after infection underwent to inter-related psychological stressor and neurobiological consequences. Specifically, the case of PACS represents a crossroad to further investigate the relationship between psychology and physiology and, according to our vantage point, how the concept of self and its baseline might represent a point of intersection between the two. On this regard, we think that future research needs to investigate the neuronal (brain imaging) correlates of psychological baseline in a sample of PACS survivors in order to investigate whether or not the functionality of the brain show similarities with what we know about other psychopathological samples of patient suffering of depression syndromes, such as major depressive disorder and bipolar disorder in a depressive phase.

Moreover, we feel the urge to investigate how the psychological baseline of depressive psychopathology can be related to a panel of circulating inflammatory biomarkers (cytokines and chemokines), which have been implicated in the immunopsychiatry of mood disorder. This data will shed new lights on the neuro-socio-ecological and inflammatory markers of the complex mind-body-brain system and will also highlight the importance of resilience and connectedness in order to navigate times of uncertainty and change. The COVID-19 pandemic has been a very important threat and it was very challenging for all humanity. However, at the same time, the study of psychological and physiological correlates of COVID-19 pandemic and more specifically on PACS is providing an opportunity to investigate the ways in which individuals adapt to stress and adversity on both a psychological and neuroscientific level highlighting the importance a higher sense of connectedness of the self with the world, for a more inclusive society and to reduce psychopathological and inflammatory reactions.

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