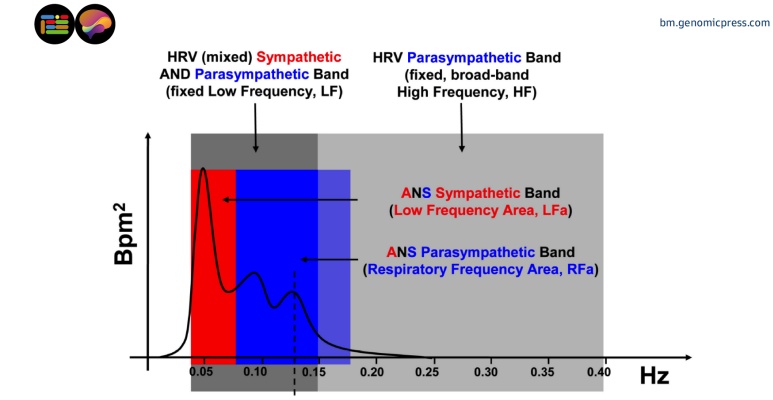
Autonomic dysfunction unmasked as a hidden driver of treatment-resistant depression

Study of 2,197 patients with resistant depression finds 95 percent improved once parasympathetic and sympathetic imbalances were identified and corrected



A spectral domain comparison of the Low Frequency area and Respiratory Frequency area (Parasympathetic and Sympathetic monitoring) method and the Low Frequency and High Frequency (Autonomic Nervous System monitoring) method.

SICKLERVILLE, NJ, UNITED STATES, March 31, 2026 /EINPresswire.com/ -- Consider a house with the water main half shut. The faucets sputter. The toilet runs all night. The garden wilts. You could call a plumber for the faucet, a landscaper for the garden, a different plumber for the toilet, and every one of them would fix something while fixing nothing. The water main stays half shut. The house stays thirsty.

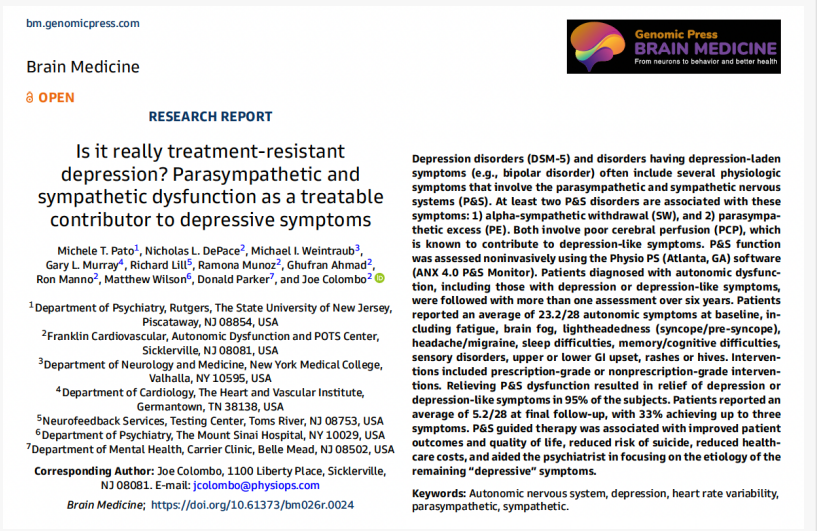
Something analogous, and far more consequential, has been happening inside the bodies of millions of people diagnosed with depression. They arrive at psychiatry offices carrying years of pharmaceutical sediment: SSRIs layered over SNRIs layered over atypical antipsychotics, dosages revised and stacked and titrated upward until the side effects rival the illness itself. Eventually somebody writes the words "treatment resistant" in a chart, and the search, for too many, ends there.

> What we found, again and again, was that these patients were not treatment resistant in any meaningful psychiatric sense. Their brains were being starved of blood."
>
> *Dr. Joe Colombo, Franklin Cardiovascular, Sicklerville, New Jersey, USA*

A new peer-reviewed study published in Brain Medicine suggests the search has been ending in the wrong place.

Blood, gravity, and the brain that cannot wait form the central narrative of the research. The study, conducted across three clinical practices in the Philadelphia, Memphis, and New York City areas over six years, followed 8,128 consecutive patients with documented autonomic dysfunction, a condition in which the involuntary nervous system fails to properly regulate basic

bodily functions. Of those, 2,197 carried prior diagnoses of depression or depression-like symptoms. They were, on average, 49.5 years old. Just under 58 percent were female. They arrived burdened not with one or two complaints but with an average of 23.2 out of 28 possible autonomic symptoms: fatigue so dense it felt architectural, brain fog that swallowed nouns mid-sentence, lightheadedness upon standing, sleep that never restored, memory lapses, gastrointestinal chaos, hormone dysregulation (especially in women's health), chronic pain, chronic headache or migraines, rashes, and sensory disturbances that made light too bright and sound too loud.



bm.genomicpress.com

Brain Medicine

OPEN

RESEARCH REPORT

Is it really treatment-resistant depression? Parasympathetic and sympathetic dysfunction as a treatable contributor to depressive symptoms

Michele T. Pato[1], Nicholas L. DePace[2], Michael I. Weintraub[3], Gary L. Murray[4], Richard Lill[5], Ramona Munoz[2], Ghufran Ahmad[2], Ron Manno[2], Matthew Wilson[6], Donald Parker[7], and Joe Colombo[2]

[1]Department of Psychiatry, Rutgers, The State University of New Jersey, Piscataway, NJ 08854, USA
[2]Franklin Cardiovascular, Autonomic Dysfunction and POTS Center, Sicklerville, NJ 08081, USA
[3]Department of Neurology and Medicine, New York Medical College, Valhalla, NY 10595, USA
[4]Department of Cardiology, The Heart and Vascular Institute, Germantown, TN 38138, USA
[5]Neurofeedback Services, Testing Center, Toms River, NJ 08753, USA
[6]Department of Psychiatry, The Mount Sinai Hospital, NY 10029, USA
[7]Department of Mental Health, Carrier Clinic, Belle Mead, NJ 08502, USA

Corresponding Author: Joe Colombo, 1100 Liberty Place, Sicklerville, NJ 08081. E-mail: jcolombo@physiops.com

Brain Medicine; https://doi.org/10.61373/bm026r.0024

Depression disorders (DSM-5) and disorders having depression-laden symptoms (e.g., bipolar disorder) often include several physiologic symptoms that involve the parasympathetic and sympathetic nervous systems (P&S). At least two P&S disorders are associated with these symptoms: 1) alpha-sympathetic withdrawal (SW), and 2) parasympathetic excess (PE). Both involve poor cerebral perfusion (PCP), which is known to contribute to depression-like symptoms. P&S function was assessed noninvasively using the Physio PS (Atlanta, GA) software (ANX 4.0 P&S Monitor). Patients diagnosed with autonomic dysfunction, including those with depression or depression-like symptoms, were followed with more than one assessment over six years. Patients reported an average of 23.2/28 autonomic symptoms at baseline, including fatigue, brain fog, lightheadedness (syncope/pre-syncope), headache/migraine, sleep difficulties, memory/cognitive difficulties, sensory disorders, upper or lower GI upset, rashes or hives. Interventions included prescription-grade or nonprescription-grade interventions. Relieving P&S dysfunction resulted in relief of depression or depression-like symptoms in 95% of the subjects. Patients reported an average of 5.2/28 at final follow-up, with 33% achieving up to three symptoms. P&S guided therapy was associated with improved patient outcomes and quality of life, reduced risk of suicide, reduced healthcare costs, and aided the psychiatrist in focusing on the etiology of the remaining "depressive" symptoms.

Keywords: Autonomic nervous system, depression, heart rate variability, parasympathetic, sympathetic.

Is it really treatment-resistant depression? Parasympathetic and sympathetic dysfunction as a treatable contributor to depressive symptoms

Every single one of them, at baseline, demonstrated measurable dysfunction of the parasympathetic and sympathetic nervous systems, the two branches of the autonomic system that together orchestrate every involuntary function the body performs. Two specific derangements emerged as the primary villains. Alpha-sympathetic withdrawal, present in 79.5 percent of the depression subpopulation, causes blood to pool in the lower extremities when a patient stands or sits up. The brain, perched at the top of the body like a penthouse apartment at the end of a failing water main, gets shorted. Parasympathetic excess, found in 54.6 percent, triggers inappropriate vasodilation (the vessels relaxing when they should be holding firm), forcing the heart to labor harder merely to keep the brain adequately supplied. Note that this can worsen in susceptible women during the menstrual cycle because fluctuations in estrogen and progesterone alter vascular tone and autonomic regulation, sometimes making it harder for the cardiovascular system to maintain adequate blood flow to the brain in the upright position. A third dysfunction, beta-sympathetic excess (27.8 percent), appeared largely as a compensatory response: the cardiac engine revving to fight gravity. All three conspire toward the same destination. Poor cerebral perfusion. A brain running on less oxygen and glucose than it requires to think, to feel, to distinguish Wednesday from the end of the world.

Understanding why the old instruments heard the wrong song requires a critical methodological distinction. Standard autonomic monitoring techniques, the kind used in most cardiology and neurology labs, measure total autonomic activity. They take the combined signal from parasympathetic and sympathetic outputs and attempt to infer each branch by approximation. It is, roughly speaking, like trying to hear two musicians in a duet by listening to the recording through a single speaker and guessing which notes belong to the violin and which to the cello.

The study team employed a different approach. P&S Monitoring adds an independent measure of respiratory activity to the standard heart rate variability signal, mathematically separating the parasympathetic from the sympathetic contribution without assumptions or approximations. The distinction is not academic. Without it, a clinician cannot determine whether the sympathetic system is genuinely overactive or merely compensating for a parasympathetic problem. Get that wrong, and your treatment does not just fail. It makes things worse.

A nervous system cannot be rushed, which is why treatment followed what the authors call a "low-and-slow" philosophy. Higher doses of medication, in this population, do not accelerate recovery. They cause more autonomic dysfunction and thereby more symptoms. The nervous system must be coaxed, not bludgeoned.

Prescription options included low-dose Midodrine (2.5 mg three times daily) for sympathetic withdrawal and low-dose Nortriptyline (10 mg, taken twelve hours before waking) for parasympathetic excess, both at homeostatic rather than therapeutic doses. For patients who could not tolerate pharmaceuticals, R-alpha-lipoic acid (600 mg three times daily) addressed sympathetic withdrawal by healing mitochondria and restoring nerve function, while six months of gentle, structured walking, no faster than two miles per hour, targeted parasympathetic excess. That walking protocol was originally developed for astronauts returning from space with deconditioned hearts. The parallel is not poetic license. The autonomic dysfunction in these patients causes the heart to behave as if it were living in zero gravity.

Note, this is why many of these patients do not receive the restorative and refreshing sleep they desire. For as soon as they lie down, their brains receive all the blood they want and "wake up and want to play," the patient wants to fall asleep. This merely exacerbates the "wired-tired" feeling most autonomic patients report.

Within three months, patients reported improved sleep. That matters enormously in a population running on empty; a single night of restorative rest can shift the entire horizon of what feels possible. Over six to nine months, most physiological symptoms receded. By the end of treatment, averaging 9 to 12 months, the average symptom count had fallen from 23.2 to 5.2 ($W = 0.00$, $p < .001$). Fatigue was relieved in 77.4 percent of patients. Sleep difficulties in 77.2 percent. Brain fog in 69.0 percent. And 33 percent of patients finished treatment with three or fewer symptoms remaining. Three. Out of twenty-eight.

"We compare the process to breaking a bad habit and establishing a good one. You cannot rush nerve retraining any more than you can rush a fracture. But when patients understand the physiology behind their suffering, when they see that their fatigue and fog have a measurable, mechanical cause, something shifts. They find hope. And hope is what keeps a person in treatment long enough for the nervous system to heal," added Dr. Colombo. Autonomic expert, Adjunct Professor of Internal Medicine, Rowan-Virtua School of Osteopathic Medicine.

The long COVID shadow looms large over these findings. Nearly half of the study cohort (48.3

percent) had been diagnosed with long- or post-COVID syndrome, a population now recognized as a vast and troubled reservoir of autonomic dysfunction. Other prominent conditions included orthostatic dysfunction (36.9 percent), hypertension (39.6 percent), and type 2 diabetes (16.9 percent). In many of these patients, the elevated blood pressure that had been medicated as a standalone cardiac problem was, in fact, compensatory, the heart working overtime to push blood past autonomic resistance and up to the brain. Treat the blood pressure without addressing the underlying imbalance, and you lower the number on the cuff while the brain goes hungrier still.

Recovery demands a kind of patience that modern medicine rarely rewards. Full rebalancing of the parasympathetic and sympathetic systems requires 15 to 24 months, and the process is fragile, easily set back by stress or illness. Only 9.6 percent of patients abandoned the program, however. The authors attribute this persistence, at least partly, to the early improvement in sleep quality and to the simple, radical act of telling patients that they were believed.

What remains uncertain deserves candid acknowledgment. The authors are forthright about the boundaries of what they can claim. This is an observational, single-group design with no explicit control group. Depressive symptoms were assessed not with standardized psychiatric rating scales such as the PHQ-9 or Hamilton but with a 28-item autonomic symptom questionnaire that overlaps with depression. The study carries referral bias, since all patients were seen in specialized autonomic dysfunction practices. It carries survivor and engagement bias, since individuals who remained in treatment for up to two years may differ fundamentally from those who left. The intensive clinician contact and explicit coaching about hope and long timelines may have introduced expectation or placebo effects. The authors themselves recommend what should come next: a blinded, randomized, controlled, crossover study comparing P&S-guided therapy plus usual care versus usual care alone, using standardized depression scales and autonomic endpoints.

"For too long, psychiatry has accepted the label of treatment-resistant depression as a verdict rather than a question. This research compels us to ask what we are actually treating. If a significant proportion of patients carrying that diagnosis have measurable autonomic dysfunction fueling their symptoms, then we have a responsibility to screen for it, to measure it, and to address it before concluding that a patient has failed treatment. Perhaps it was not the patient who failed. Perhaps the diagnostic framework failed them," said Dr. Michele T. Pato, first author of the study, from the Department of Psychiatry at Rutgers, The State University of New Jersey.

The body must be heard before the mind can be read. What this study describes is not a replacement for psychiatric care. It is something potentially more consequential: a physiological foundation that must be laid before psychiatric care can land where it belongs. Once autonomic function is restored and cerebral perfusion normalized, any symptoms that remain are, by definition, true end-organ psychiatric illness, and they can finally be treated in a focused and individualized manner. The mind, it turns out, cannot be accurately read while the body is still

shouting.

The work spans cardiology, neurology, and autonomic medicine, and it points toward a future in which the borders between those disciplines and psychiatry grow thinner. For the millions of patients currently warehoused behind the label treatment resistant, that thinning cannot arrive soon enough.

The peer-reviewed research article in Brain Medicine titled "Is it really treatment-resistant depression? Parasympathetic and sympathetic dysfunction as a treatable contributor to depressive symptoms," is freely available via Open Access, starting on 31 March 2026 in Brain Medicine at the following hyperlink: https://doi.org/10.61373/bm026r.0024

The full reference for citation purposes is: Pato MT, DePace NL, Weintraub MI, Murray GL, Lill R, Munoz R et al. Is it really treatment-resistant depression? Parasympathetic and sympathetic dysfunction as a treatable contributor to depressive symptoms. Brain Medicine 2026. DOI: https://doi.org/10.61373/bm026r.0024. Epub 2026 Mar 31.

About Brain Medicine: Brain Medicine (ISSN: 2997-2639, online and 2997-2647, print) is a peer-reviewed medical research journal published by Genomic Press, New York. Brain Medicine is a new home for the cross-disciplinary pathway from innovation in fundamental neuroscience to translational initiatives in brain medicine. The journal's scope includes the underlying science, causes, outcomes, treatments, and societal impact of brain disorders, across all clinical disciplines and their interface.

Visit the Genomic Press Virtual Library: https://issues.genomicpress.com/bookcase/gtvov/

Our media website is at: https://media.genomicpress.com/

Our full website is at: https://genomicpress.com/

Ma-Li Wong
Genomic Press
mali.wong@genomicpress.com
Visit us on social media:
X
LinkedIn
Bluesky
Instagram
Facebook

---

we have missed, please do bring it to our attention. Your help is welcome. EIN Presswire, Everyone's Internet News Presswire™, tries to define some of the boundaries that are reasonable in today's world. Please see our Editorial Guidelines for more information.