

EPIGENETIC MODIFICATIONS OF DNA METHYLATION IN LYMPHOCYTES EXPOSED TO GALACTIC COSMIC RADIATION: A TWIN STUDY WITHIN THE NASA TWINS STUDY PROGRAM

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Abstract: The NASA Twins Study is a singular experiment: one identical twin spent a year aboard the International Space Station while his genetically identical brother remained on the ground, and the comparison between them isolated the biology of spaceflight from the confound of genetic difference. Among the changes the study documented were alterations in DNA methylation in the astronaut's immune cells, near genes governing immune function. Those changes have since been cited as evidence of how galactic cosmic radiation rewrites the epigenome. This article argues that the citation outruns the evidence. The Twins Study has a sample of one twin pair, and the spaceflight environment it sampled bundles galactic cosmic radiation together with microgravity, isolation, sleep disruption, elevated carbon dioxide, and altered diet — so a methylation change observed in the flown twin cannot, on the study's design, be assigned to radiation rather than to any other component of the bundle. Compounding this, the International Space Station orbits within the protection of Earth's magnetosphere, where the galactic cosmic radiation dose is a fraction of what a crew bound for Mars would receive. The original contribution of this article is the Spaceflight–Radiation Methylation Corpus, the first cross-study catalogue of differentially methylated immune-cell loci and functional pathways assembled from eighteen Scopus-indexed studies and cross-classified by exposure source — the spaceflight bundle, isolated ionizing radiation, and galactic-cosmic-radiation analog irradiation — and by post-exposure reversibility. The corpus permits, for the first time, a side-by-side reading: a radiation-specific methylation signature, concentrated in DNA-damage-response loci, oxidative-stress genes, and repetitive-element hypomethylation, is partially separable from a spaceflight-general signature concentrated in immune-activation and inflammatory pathways. Read against the corpus, the Twins Study lymphocyte methylation changes overlap predominantly with the spaceflight-general signature, and most reverted after return to Earth. The corpus reframes the interpretive task from detecting a methylation change to locating it within an exposure-resolved and reversibility-resolved reference frame.

Keywords: *DNA methylation, galactic cosmic radiation, lymphocytes, NASA Twins Study, epigenetics, exposure attribution, spaceflight-radiation methylation corpus.*

INTRODUCTION

The NASA Twins Study was built around a piece of biological luck. NASA's astronaut corps included a pair of identical twins, Scott and Mark Kelly, and when Scott was assigned a year-long mission aboard the International Space Station, the agency had the rare opportunity to run a controlled experiment on a human being. One twin flew; the other stayed home. Because the two share a genome, any biological divergence measured between them across the mission could be attributed to the environment rather than to inherited difference. Ten research teams profiled the twins across multiple biological systems, and the integrated analysis was published as a landmark multidimensional study (Garrett-Bakelman et al., 2019). Among its many findings was one that concerns the present article directly: the flown twin's immune cells showed alterations in DNA methylation near genes governing immune function, alterations not seen in the ground twin.

DNA methylation is the most studied of the epigenetic marks. A methyl group attached to a cytosine, almost always where a cytosine precedes a guanine, can silence or modulate the gene nearby without altering the underlying sequence. Methylation patterns are laid down during development, maintained through cell division, and — importantly for this article — remodeled in response to the environment. Ionizing radiation is one of the environmental agents known to remodel them: across cell culture, animal models, and exposed human populations, radiation has been shown to shift both genome-wide methylation levels and the methylation of specific loci (Belli & Tabocchini, 2020; Ma et al., 2025). It is therefore natural, on first reading, to connect the two facts — radiation remodels methylation, and the flown twin's methylation changed — and to conclude that the space radiation environment rewrote the astronaut's epigenome.

This article argues that the connection, natural as it is, is not licensed by the evidence, and that treating it as licensed has consequences for how the risk of deep-space radiation is assessed. The argument turns on two features of the Twins Study that are easy to acknowledge in passing and hard to keep in view. The first is the sample size. The Twins Study is a study of one twin pair. It is an N-of-1 experiment, and an N-of-1 experiment, however carefully instrumented, cannot establish that an observed change is typical rather than idiosyncratic. The second feature is confounding. The spaceflight environment is not a radiation exposure; it is a bundle of simultaneous stressors — microgravity, galactic cosmic radiation, social isolation and confinement, disrupted circadian rhythm and sleep, chronically elevated cabin carbon dioxide, and an altered diet. A methylation change measured in the flown twin is a response to the whole bundle. Nothing in the study's design separates the radiation component from the rest.

A third feature sharpens the problem specifically for radiation. The International Space Station orbits at an altitude of roughly 400 kilometers, well inside the Earth's magnetosphere, which deflects a large fraction of the charged particles that make up galactic cosmic radiation. The radiation environment the Kelly twin experienced is real and elevated relative to the ground, but it is not the radiation environment of deep space. A crew in transit to Mars, beyond the magnetosphere's protection, would receive a galactic-cosmic-radiation dose several times higher and of a different particle composition (NASA Human Research Program, 2023). The Twins Study, in other words, is not even a strong proxy for the exposure its findings are most often invoked to illuminate.

The research question of this article is consequently an attribution question. Given a documented DNA methylation change in the lymphocytes of a spaceflight-exposed individual, what is required to attribute that change specifically to galactic cosmic radiation rather than to the broader spaceflight bundle, and does the existing evidence — the Twins Study foremost among it — meet that requirement? Three hypotheses structure the analysis. The first holds that the methylation changes documented by the Twins Study cannot be attributed specifically to galactic

cosmic radiation, because the study's bundled exposure and N-of-1 design provide no mechanism for isolating the radiation contribution. The second holds that, when methylation findings from spaceflight are placed alongside findings from isolated ionizing radiation in a common reference frame, a radiation-specific signature becomes partially separable from a spaceflight-general one, and that the Twins Study lymphocyte changes overlap predominantly with the latter. The third holds that the reversibility of a methylation change — whether it reverts after the exposure ends or persists — is a more informative readout for crew health than the mere fact of the change, and that the spaceflight methylation literature, read carefully, shows a reversibility gradient rather than a uniform response.

The original contribution of this article is the construction of that common reference frame, which I term the Spaceflight–Radiation Methylation Corpus. The corpus is a curated cross-study catalogue: it assembles, from the eighteen Scopus-indexed studies identified in the literature search, the differentially methylated immune-cell loci and functional pathways that each study reports, and it cross-classifies every entry along two axes — the exposure source responsible (the spaceflight bundle, isolated ionizing radiation, or galactic-cosmic-radiation analog irradiation) and the reversibility of the change after the exposure ends. Such a catalogue does not exist in the literature; spaceflight methylation findings and radiation methylation findings are reported in separate bodies of work that rarely cite one another, and no resource places them in a single exposure-resolved frame. The corpus is the contribution. It is a resource rather than a measurement, a model rather than a metric, and its value is that it converts an unanswerable question — did radiation cause this change? — into an answerable one: does this change sit where the radiation-specific signature sits, or where the spaceflight-general signature sits?

The article proceeds as follows. The next section reviews the literature on DNA methylation in spaceflight and under ionizing radiation and describes the methodology used to assemble the corpus. A Research Results section presents the corpus itself, organized as a catalogue of functional locus categories. Three analytical sections then develop the argument: the attribution problem in the Twins Study, the separation of the radiation-specific and spaceflight-general signatures that the corpus makes visible, and the reversibility gradient and what it implies for crew health monitoring. The conclusion returns to the three hypotheses and states the corpus's limitations and the work needed to extend it.

LITERATURE REVIEW AND METHODOLOGY

Literature Review

The literature relevant to this article comes from two communities that have, until recently, worked largely in parallel: the spaceflight-omics community and the radiation-epigenetics community. A central purpose of the corpus is to make their findings commensurable, and the review below treats them in turn.

The spaceflight-omics literature begins, for present purposes, with the Twins Study itself (Garrett-Bakelman et al., 2019). Its epigenetic component reported that DNA methylation shifted in the flown twin during the mission, with changes near immune-related genes, and — a point often underemphasized — that the overall magnitude of methylation change in the flown twin was not dramatically greater than the variation seen in the ground twin over the same period, and that most flight-associated changes had returned toward baseline by the post-flight sampling. The Twins Study was followed by a coordinated set of analyses that broadened the picture. Da Silva et al. (2020) integrated transcriptomic, proteomic, metabolomic, and epigenetic data across many spaceflight datasets, including those aggregated in NASA's GeneLab and Open Science Data

Repository (National Aeronautics and Space Administration, 2024), and identified mitochondrial stress as a recurrent hub, with inflammation and immune dysregulation as consistent accompaniments. Gertz et al. (2020) profiled astronaut peripheral blood at single-cell resolution and documented spaceflight-associated changes in immune cell composition and gene regulation. The telomere work of Luxton et al. (2020) and the companion analysis of Luxton, McKenna, and colleagues (2020) established that telomere length and DNA-damage-response markers behave distinctively in the spaceflight environment, lengthening in flight and shortening rapidly on return, with signatures the authors linked to chronic oxidative and radiation stress.

More recent spaceflight work has extended the epigenetic picture to commercial missions and larger data resources. The Space Omics and Medical Atlas assembled a broad multi-omic compendium across orbits (Overbey et al., 2024), and single-cell multi-ome profiling of the Inspiration4 civilian crew identified a reproducible spaceflight gene-expression signature enriched in oxidative phosphorylation and immune pathways (Kim et al., 2024). RNA-level epigenetic modification has entered the picture as well, with direct sequencing of astronaut blood revealing a post-flight spike in N6-methyladenosine RNA methylation (Grigorev et al., 2024). Epigenetic-aging analyses have become a distinct strand: spaceflight has been shown to accelerate epigenetic age transiently, with the acceleration largely reversing after return (Fuentelba et al., 2026), and aging and frailty biomarkers more broadly are altered by the spaceflight environment (Camera et al., 2024). A longitudinal transcriptomic and epigenetic analysis of two astronauts reported methylation changes partitioned into transient and persistent classes (Ao et al., 2025). Ground analogs contribute a controlled counterpart: the Mars-500 isolation experiment, which reproduced the confinement and isolation of a long mission without the radiation, showed measurable methylation dynamics (Hou et al., 2022) and a longitudinal epigenetic-aging response (Nwanaji-Enwerem et al., 2020). The Mars-500 studies are analytically valuable precisely because they isolate the isolation-and-confinement component of the spaceflight bundle from the radiation component.

The radiation-epigenetics literature is older and, in the relevant respects, better controlled, because it can deliver a defined radiation dose in the absence of the other spaceflight stressors. Belli and Tabocchini (2020) reviewed the mechanisms by which ionizing radiation produces epigenetic modifications and their relevance to radiation protection, and Ma et al. (2025) surveyed the genome-wide DNA methylation responses to ionizing radiation and their candidacy as radiation biomarkers. A consistent finding across this literature is that radiation tends to produce global hypomethylation — a loss of methylation at repetitive elements such as the LINE-1 sequences — alongside locus-specific gains at particular promoters. The occupational evidence is directly relevant to the present article's focus on lymphocytes: Isubakova et al. (2021) measured promoter methylation of apoptosis-regulating genes in the blood lymphocytes of workers chronically exposed to occupational gamma radiation, and found correlations between specific promoter methylation and the burden of chromosomal aberrations. For the high-energy heavy ions that dominate galactic cosmic radiation, the most directly relevant work is experimental: Perdyan et al. (2024) showed that high-linear-energy-transfer iron ions induce a persistent increase in DNA methylation, whereas lower-energy silicon ions and X-rays induce a decrease that does not persist — a result that demonstrates, importantly, that radiation quality, not just dose, shapes the methylation response. Bertucci et al. (2021) showed in a vertebrate model that ionizing radiation disrupts the normal epigenetic-aging trajectory, accelerating it at some loci and decelerating it at others.

Reading the two literatures together exposes the gap this article addresses. The spaceflight literature reports methylation changes and attributes them, loosely, to “spaceflight” or, more loosely still, to “space radiation.” The radiation literature reports methylation changes under defined doses and qualities of radiation, in the absence of the spaceflight bundle. The two are rarely

cross-referenced, and there is no resource that places a spaceflight-reported methylation change next to a radiation-reported one to ask whether they coincide. Without such a resource, the attribution question at the center of this article cannot even be posed precisely, let alone answered. The Spaceflight–Radiation Methylation Corpus is built to fill exactly that gap.

Research Methodology

The methodology is that of structured corpus assembly. The article does not generate new methylation data; it builds a curated, cross-classified catalogue from published findings and then reads the Twins Study against it. The work proceeded in four steps.

The first step was source selection and extraction. From the eighteen Scopus-indexed studies identified in the literature search — spanning spaceflight omics, ground-analog isolation, occupational radiation exposure, and controlled heavy-ion irradiation — I extracted every reported finding of differential DNA methylation in immune cells, blood, or directly relevant cell models. For each finding I recorded the functional category of the affected locus or pathway, the direction of the methylation change where the source reported it, the exposure that produced it, and, where the source reported follow-up sampling, whether the change reverted or persisted after the exposure ended. To keep the corpus honest, entries were held at the level of functional locus category — for example, DNA-double-strand-break repair genes, or repetitive-element global methylation — rather than at the level of individual cytosine sites, because category-level findings are what the heterogeneous source studies reliably support and because site-level claims would imply a precision the assembled literature does not have.

The second step was the cross-classification that gives the corpus its structure. Every entry was assigned to one of three exposure sources. The first, the spaceflight bundle, denotes findings from actual spaceflight, in which radiation is inseparable from microgravity, isolation, and the other stressors. The second, isolated ionizing radiation, denotes findings from occupational exposure or from cell and animal models receiving a defined radiation dose without the spaceflight bundle. The third, galactic-cosmic-radiation analog, denotes findings from controlled irradiation with the high-linear-energy-transfer heavy ions that approximate the most damaging component of galactic cosmic radiation. Every entry was also classified, where the evidence allowed, as predominantly reversible or predominantly persistent after the exposure ended. The corpus is the matrix that results: functional categories down the side, exposure sources and reversibility across it.

The third step was the reading of the Twins Study against the assembled corpus. With the corpus in place, the immune-cell methylation changes reported by Garrett-Bakelman et al. (2019) could be located within it — assigned to functional categories and compared, category by category, against which exposure sources independently produce changes in those same categories. This is the step that converts the attribution question into a tractable one. If a Twins Study change falls in a category that isolated ionizing radiation and galactic-cosmic-radiation analogs also mark, the radiation attribution gains support; if it falls in a category marked by the spaceflight bundle and by non-radiation analogs such as Mars-500 isolation, the radiation attribution loses support.

The fourth step was the explicit statement of what the corpus can and cannot do, and it is a step I want to foreground rather than bury. The corpus is a synthesis of heterogeneous studies that used different platforms, cell preparations, doses, and analytic pipelines; it harmonizes them at the level of functional category, and that harmonization is interpretive, not mechanical. The corpus cannot prove that a given Twins Study change was or was not caused by radiation; an N-of-1 study cannot be rescued by a corpus. What the corpus can do is make the attribution claim auditable — it shows where a change sits relative to exposure-resolved evidence, and it thereby

replaces an assertion with a placement. A reader who disagrees with a particular classification can see exactly which entry and which source are in dispute. That auditability, not a false promise of resolution, is what the corpus offers. Its limitations are revisited in the conclusion.

RESEARCH RESULTS

The assembled Spaceflight–Radiation Methylation Corpus is presented as Table 1, organized into four functional groups of immune-cell loci. The corpus and its reading produce three results.

The first result is the structure of the corpus itself. Across the four functional groups — immune activation and inflammation, DNA damage response and genomic maintenance, oxidative stress and mitochondrial function, and cellular aging and apoptosis — the exposure sources do not mark the groups uniformly. Two groups are marked by all three exposure sources: the DNA-damage-response group and the oxidative-stress group carry entries from the spaceflight bundle, from isolated ionizing radiation, and from galactic-cosmic-radiation analog irradiation. Two groups are marked predominantly by the spaceflight bundle and by non-radiation analogs: the immune-activation-and-inflammation group and, in part, the cellular-aging group carry entries from spaceflight and from the Mars-500 isolation analog, but are not the categories that controlled radiation studies most prominently mark. This uneven marking is the corpus's central structural finding, and it is the basis for distinguishing two signatures.

The second result is the distinction itself. A radiation-specific methylation signature is partially separable in the corpus: it is concentrated in the DNA-damage-response loci, in oxidative-stress-response genes, and — most distinctively — in the hypomethylation of repetitive elements such as the LINE-1 sequences, a change that controlled radiation studies report consistently (Belli & Tabocchini, 2020; Ma et al., 2025) and that the heavy-ion work attaches specifically to high-linear-energy-transfer particles (Perdyan et al., 2024). A spaceflight-general signature is separable alongside it: it is concentrated in immune-activation and inflammatory pathways, the categories the Twins Study most prominently reported (Garrett-Bakelman et al., 2019) and that the Mars-500 isolation analog also marks despite carrying no meaningful radiation exposure (Hou et al., 2022; Nwanaji-Enwerem et al., 2020). The separation is partial, not clean — the oxidative-stress category is marked by both signatures, which is expected, since several spaceflight stressors converge on oxidative stress — but it is real, and it is visible only because the corpus places the two literatures in one frame.

The third result is the reading of the Twins Study against this structure. The immune-cell methylation changes that Garrett-Bakelman et al. (2019) reported fall predominantly in the immune-activation-and-inflammation group — that is, in the spaceflight-general signature rather than in the radiation-specific one. They do not fall predominantly in the repetitive-element-hypomethylation category that most cleanly marks isolated radiation exposure. Moreover, the Twins Study itself reported that the large majority of the flight-associated methylation changes reverted toward baseline after return to Earth, which aligns the Twins Study findings with the reversible class in the corpus's reversibility axis. Both placements point the same way: the Twins Study lymphocyte methylation changes sit where the spaceflight bundle sits, not where isolated galactic cosmic radiation sits, and they sit predominantly in the reversible class.

Functional locus category	Methylation change	Exposure source(s) documenting it	Reversibility
Group A — Immune activation and inflammation (spaceflight-general signature)			
Adaptive immunity / T-cell regulatory genes	Locus-specific shift	Spaceflight bundle; isolation analog	Predominantly reversible
Innate immune response genes	Locus-specific shift	Spaceflight bundle; isolation analog	Predominantly reversible
Inflammatory cytokine pathway genes	Locus-specific shift	Spaceflight bundle	Mixed
Group B — DNA damage response and genomic maintenance (radiation-specific signature)			
DNA double-strand-break repair genes	Locus-specific gain	Isolated ionizing radiation; GCR analog	Mixed
Repetitive elements (LINE-1, satellite): global methylation	Hypomethylation	Isolated ionizing radiation; GCR analog	Predominantly persistent
Telomere-maintenance-associated loci	Locus-specific shift	Spaceflight bundle; GCR analog	Mixed
Group C — Oxidative stress and mitochondrial function (shared signature)			
Oxidative-stress response genes	Locus-specific shift	Spaceflight bundle; isolated ionizing radiation; GCR analog	Mixed
Mitochondrial function genes	Locus-specific shift	Spaceflight bundle	Predominantly reversible
Group D — Cellular aging and apoptosis			
Apoptosis-regulating gene promoters	Promoter methylation shift	Isolated ionizing radiation (lymphocytes)	Predominantly persistent
Epigenetic-aging-clock CpG sites	Net age-estimate shift	Spaceflight bundle; isolation analog; GCR analog	Predominantly reversible

Table 1. The Spaceflight–Radiation Methylation Corpus: immune-cell differentially methylated locus categories, cross-classified by exposure source and post-exposure reversibility.

The corpus is a literature-derived synthesis held at the level of functional locus category. Entries are supported by Garrett-Bakelman et al. (2019), Belli and Tabocchini (2020), Ma et al. (2025), Perdyan et al. (2024), Isubakova et al. (2021), Hou et al. (2022), Nwanaji-Enwerem et al. (2020), Luxton et al. (2020), Bertucci et al. (2021), and Ao et al. (2025). “GCR analog” denotes controlled high-linear-energy-transfer heavy-ion irradiation. Reversibility classifications apply where the source studies reported post-exposure follow-up; “mixed” indicates that both reverting and persistent loci are reported within the category.

One feature of the corpus warrants a separate comment because it qualifies the third result. The reversibility axis is the least uniformly populated of the two classifications, because many of the source studies did not sample long enough after exposure to determine whether a change reverted or persisted. Where follow-up exists, a gradient is visible rather than a dichotomy:

immune-activation and mitochondrial categories revert most readily, repetitive-element hypomethylation tends to persist, and the DNA-damage-response and oxidative-stress categories are genuinely mixed. The corpus records this gradient honestly, including the gaps, and the gaps are themselves a finding — they mark where the literature has not yet looked.

THE ATTRIBUTION PROBLEM IN THE NASA TWINS STUDY

The Twins Study is a remarkable experiment, and the first task of this section is to say clearly what makes it remarkable, because the attribution critique that follows is not a criticism of the study but a clarification of what it can support.

What makes the Twins Study remarkable is the control of the genetic variable. In any ordinary comparison of a spaceflight-exposed person with an unexposed person, genetic difference between the two individuals confounds the comparison: a methylation difference might reflect the exposure or might reflect that the two people simply have different genomes and different epigenetic baselines. Identical twins remove that confound. Scott and Mark Kelly share a genome, so a methylation divergence measured between them across the mission is, to a first approximation, environmental in origin. This is a genuine and valuable piece of experimental control, and the Twins Study exploited it as fully as a single twin pair allows (Garrett-Bakelman et al., 2019).

But the control of the genetic variable is not the control of the exposure variable, and the two are easy to conflate. Removing genetic difference licenses the inference that a divergence is environmental. It does not license any inference about which environmental factor is responsible. And here the structure of the spaceflight environment becomes decisive. Spaceflight is not a single exposure; it is a tightly bundled set of simultaneous stressors. The flown twin experienced microgravity, galactic cosmic radiation, fifteen months of confinement and social isolation, a disrupted light-dark cycle and degraded sleep, chronically elevated cabin carbon dioxide, a restricted and altered diet, and the physiological stress of launch and return. All of these acted on him at once, for the same duration, with no possibility of separating them. A methylation change measured at the end of the mission is a response to the bundle. The study design contains no lever that isolates the radiation component.

Consider what would be required to isolate it. To attribute a methylation change specifically to galactic cosmic radiation, one would need either to vary the radiation exposure while holding the rest of the bundle constant — which the Twins Study did not and could not do — or to compare the spaceflight result against a matched exposure that includes every component of the bundle except radiation. The second comparison is, in fact, partially available, and it is one of the reasons the corpus includes the Mars-500 isolation analog. Mars-500 placed a crew in 520 days of confinement and isolation, reproducing the psychological and circadian components of the spaceflight bundle, on the ground, with no spaceflight radiation exposure. The Mars-500 participants nonetheless showed measurable DNA methylation dynamics (Hou et al., 2022) and an epigenetic-aging response (Nwanaji-Enwerem et al., 2020). That is a critical control result. It demonstrates that the isolation-and-confinement component of the bundle, entirely by itself, remodels methylation. Any methylation change observed in a flown astronaut that also appears in a Mars-500 participant cannot be claimed for radiation, because the Mars-500 participant received none.

The N-of-1 problem compounds the attribution problem rather than standing apart from it. Even if the spaceflight bundle could somehow be decomposed, a study of one twin pair could not establish that the decomposition generalizes. Epigenetic responses vary between individuals; a single astronaut's methylation trajectory might be representative of astronauts in general or might be particular to him. The Twins Study authors were themselves careful on this point, noting

the single-subject limitation explicitly, and noting too that the magnitude of methylation change in the flown twin was not greatly outside the range of variation seen in the ground twin over the same period. The later commercial-spaceflight studies have begun to add subjects — the Inspiration4 crew of four (Kim et al., 2024; Grigorev et al., 2024), the two-astronaut longitudinal analysis (Ao et al., 2025), the Axiom-2 crew (Fuentelba et al., 2026) — and this is genuine progress, but the combined flown sample with methylation data remains small, and almost all of it is from low Earth orbit.

This last fact returns the argument to galactic cosmic radiation specifically. The International Space Station sits inside the magnetosphere, which deflects much of the charged-particle flux of galactic cosmic radiation. The dose an ISS crew member receives is elevated relative to the ground but is a fraction of the dose a crew beyond the magnetosphere would receive, and the particle spectrum differs as well (NASA Human Research Program, 2023; United Nations Scientific Committee on the Effects of Atomic Radiation, 2021). The heavy-ion experiments in the corpus exist precisely because the deep-space radiation environment cannot be sampled by an ISS mission. So the Twins Study, when invoked as evidence about galactic cosmic radiation, is being asked to speak about an exposure it did not deliver — a low-Earth-orbit radiation environment is standing proxy for a deep-space one. The first hypothesis is, on this analysis, confirmed: the Twins Study methylation changes cannot be attributed specifically to galactic cosmic radiation, both because the bundled design cannot isolate the radiation component and because the radiation component it did sample is not the deep-space exposure of interest.

SEPARATING THE RADIATION-SPECIFIC AND SPACEFLIGHT-GENERAL SIGNATURES

If the Twins Study alone cannot attribute a methylation change to radiation, the question becomes whether the broader literature can do better when its findings are read together. The corpus is the instrument for that reading, and this section develops what it shows.

The logic is one of triangulation. No single study isolates galactic cosmic radiation from the spaceflight bundle, but different studies hold different variables fixed, and the pattern across them is informative in a way that no one of them is alone. Controlled irradiation studies deliver a defined radiation dose with none of the spaceflight bundle: their methylation findings are radiation findings, full stop. Occupational-exposure studies deliver chronic radiation to humans, again without the spaceflight bundle: Isubakova et al. (2021) measured promoter methylation of apoptosis-regulating genes in the lymphocytes of radiation workers and tied it to chromosomal-aberration burden, a clean human-lymphocyte radiation result. Heavy-ion experiments deliver the specific high-linear-energy-transfer particles that dominate galactic cosmic radiation: Perdyan et al. (2024) showed that iron ions induce a persistent methylation increase distinct from the response to X-rays. And the Mars-500 analog delivers the spaceflight bundle minus radiation. Lay these alongside the actual spaceflight findings, and a methylation change that appears under controlled radiation and under heavy ions but not under Mars-500 isolation is a candidate radiation-specific change; a change that appears under spaceflight and under Mars-500 isolation but not prominently under controlled radiation is a candidate spaceflight-general change.

Run through the corpus, this triangulation yields the two signatures named in the Results. The radiation-specific signature is anchored most firmly by repetitive-element hypomethylation. The loss of methylation at LINE-1 and satellite sequences is one of the most consistent findings in the radiation-epigenetics literature (Belli & Tabocchini, 2020; Ma et al., 2025), it is dose-related in occupational cohorts, and the heavy-ion work attaches a persistent methylation change specifically to high-linear-energy-transfer particles (Perdyan et al., 2024). It is not a prominent finding

of the Mars-500 isolation analog. Repetitive-element hypomethylation is, in the corpus, the closest thing to a radiation fingerprint. The DNA-damage-response and oxidative-stress categories also carry radiation marking, consistent with the direct mechanism by which ionizing radiation acts — clustered DNA damage and reactive-oxygen-species generation — and the telomere and DNA-damage signatures that Luxton et al. (2020) linked to chronic radiation stress in flown astronauts belong here.

The spaceflight-general signature is anchored by the immune-activation and inflammatory categories. These are the categories the Twins Study most prominently reported (Garrett-Bakelman et al., 2019), and they are also marked by the Mars-500 isolation analog (Hou et al., 2022; Nwanaji-Enwerem et al., 2020), which is the discriminating fact: an immune-pathway methylation change that appears in a confined, isolated, but unirradiated Mars-500 participant is being driven by something other than radiation — by the physiological stress of confinement, by circadian disruption, by the immune consequences of altered sleep. Da Silveira et al. (2020) and Kim et al. (2024) both identify inflammation and immune dysregulation as central, recurrent features of the spaceflight response across many datasets, and the corpus reads those features as spaceflight-general rather than radiation-specific.

The honest qualification is that the separation is partial. The oxidative-stress category is marked by both signatures, and this is not a defect of the corpus but a fact about biology: radiation generates reactive oxygen species, but so do psychological stress, circadian disruption, and microgravity-associated mitochondrial dysfunction (da Silveira et al., 2020). A methylation change in an oxidative-stress gene is genuinely ambiguous, and the corpus marks it as ambiguous rather than forcing it into one signature. Likewise, the epigenetic-aging-clock category is marked by all three exposure sources, because epigenetic age responds to the whole spectrum of stressors (Fuentelba et al., 2026; Camera et al., 2024; Bertucci et al., 2021). The corpus does not manufacture a clean dichotomy where the biology provides a gradient. But the two ends of the gradient are real, and the central reading stands: the Twins Study lymphocyte methylation changes cluster at the spaceflight-general end. The second hypothesis is supported. It is supported with the explicit caveat that “supported” here means “located by triangulation,” not “proven by isolation” — the corpus improves the attribution, it does not complete it.

It is worth drawing out why this matters beyond the bookkeeping. If the immune-pathway methylation changes seen in flown astronauts are largely spaceflight-general — driven substantially by confinement, stress, and circadian disruption — then two consequences follow. The first is for the Twins Study's legacy: its epigenetic findings are better read as evidence about the integrated human response to the spaceflight environment than as evidence about radiation, and the frequent shorthand that compresses them into a radiation story is a misreading. The second is for deep-space risk assessment: the genuinely radiation-specific changes — repetitive-element hypomethylation, persistent DNA-damage-response marking — are exactly the changes that low-Earth-orbit missions sample weakly and that a Mars transit would amplify. The corpus suggests that the radiation-epigenetics risk for a Mars crew is real but is poorly indexed by the spaceflight findings most often cited for it, and is better indexed by the heavy-ion experiments that the spaceflight-omics discourse cites least.

THE REVERSIBILITY GRADIENT AND ITS MEANING FOR CREW HEALTH

A methylation change can be alarming or trivial depending on a property the corpus tracks on its second axis: whether the change reverts when the exposure ends. This section develops the third hypothesis — that reversibility, not the bare presence of a change, is the health-relevant readout. The intuition is straightforward. The epigenome is, by design, responsive to the

environment; that responsiveness is what allows cells to adjust gene expression to circumstances. A methylation change that appears during an exposure and disappears afterward is, in many cases, exactly the adaptive response the system is built to produce, and its appearance is not in itself a sign of damage. A methylation change that persists long after the exposure has ended is a different matter: persistence is what converts an acute response into a lasting alteration of the cell's regulatory state, and it is persistent changes that carry the plausible long-term health implications, including the elevated cancer risk that radiation epigenetics has long been concerned with and that low-dose risk-assessment frameworks attempt to bound (Belli & Tabocchini, 2020; National Council on Radiation Protection and Measurements, 2020). The bare fact that methylation changed during a mission therefore tells us much less than the question of whether it changed back.

The Twins Study itself supplies the most directly relevant data point, and it is one that the radiation-story shorthand tends to omit. The study reported that the large majority of the flight-associated methylation changes in the flown twin reverted toward baseline after his return to Earth — a finding emphasized in the contemporary summaries of the study, which noted that the astronaut showed no major lasting epigenetic divergence from his ground-based brother. On the corpus's reversibility axis, the Twins Study immune-pathway changes fall in the reversible class. This aligns with the reversibility behavior of the spaceflight-general signature more broadly: epigenetic-age acceleration during spaceflight has been shown to reverse after return (Fuentelba et al., 2026), and the two-astronaut longitudinal analysis explicitly partitioned methylation changes into transient and persistent classes, with a substantial transient component (Ao et al., 2025). The immune-activation and mitochondrial categories, in the corpus, are the ones that revert most readily.

The radiation-specific signature behaves differently, and this is the corpus reading that matters most for deep-space planning. Repetitive-element hypomethylation, the closest thing the corpus has to a radiation fingerprint, tends to persist; the heavy-ion work documents a methylation increase from high-linear-energy-transfer iron ions that is specifically described as persistent over time, in contrast to the non-persistent response to X-rays (Perdyan et al., 2024). The occupational-exposure finding sits here too: Isubakova et al. (2021) measured apoptosis-gene promoter methylation in radiation workers years into chronic exposure, and the correlation with accumulated chromosomal aberrations is a signature of a change that has not reverted. The reversibility gradient in the corpus is therefore not random with respect to the two signatures: the spaceflight-general signature reverts preferentially, and the radiation-specific signature persists preferentially. That is a coherent and, I think, an important pattern, though I hold it with appropriate caution because the reversibility axis is, as the Results noted, the corpus's most sparsely populated dimension.

The operational implication is a reorientation of what crew epigenetic monitoring should measure. A monitoring program that records whether an astronaut's methylation changed during a mission is recording something that is expected, largely adaptive, and on current evidence largely reversible. A monitoring program designed around the corpus would do something more specific: it would track the radiation-specific categories — repetitive-element methylation above all — and it would weight a finding by its position on the reversibility axis, treating a persistent change in a radiation-specific category as the signal that warrants concern and a reverting change in a spaceflight-general category as the expected background. For a Mars transit, where the radiation exposure is the component that low-Earth-orbit experience least prepares us for, this reorientation is not academic. It identifies the measurement — longitudinal repetitive-element methylation, sampled well after return, not merely during flight — that would actually index the deep-space epigenetic risk.

A methodological reflection belongs here, since the corpus is this article's contribution and its reversibility axis is its weakest part. The honest position is that the corpus currently establishes the reversibility gradient as a hypothesis well grounded in the available follow-up data, not as a settled result, because too many source studies stopped sampling too soon. I have marked every category where the reversibility evidence is thin as “mixed” rather than forcing a classification, and I would rather the corpus show its gaps than paper over them. The gaps are, in their own way, the corpus's most actionable output: they are a specification of the longitudinal sampling that the field has not yet done and should.

CONCLUSION

The NASA Twins Study earned its prominence honestly. It is the only controlled human experiment that has ever isolated the biology of spaceflight from the confound of genetic difference, and its epigenetic component genuinely showed that DNA methylation in an astronaut's immune cells shifts across a year-long mission. This article has not disputed any of that. It has disputed only the further step — taken not by the study's authors but by its frequent secondary readings — that compresses those findings into evidence about galactic cosmic radiation.

The first hypothesis held that the Twins Study methylation changes cannot be attributed specifically to galactic cosmic radiation. It is confirmed, on two independent grounds. The study's exposure is a bundle in which radiation is inseparable from microgravity, isolation, circadian disruption, and the rest, and the N-of-1 twin-pair design contains no lever to decompose the bundle. And the radiation the study did sample was the low-Earth-orbit environment inside the magnetosphere, not the deep-space galactic-cosmic-radiation environment its findings are invoked to illuminate. The Mars-500 isolation analog seals the argument: it shows that confinement alone, with no spaceflight radiation, remodels methylation, so any spaceflight methylation change that also appears under Mars-500 isolation cannot be claimed for radiation.

The second hypothesis held that a radiation-specific signature becomes partially separable from a spaceflight-general one when the literatures are placed in a common frame, and that the Twins Study changes fall on the spaceflight-general side. It is supported by the corpus. The radiation-specific signature is anchored by repetitive-element hypomethylation and DNA-damage-response marking; the spaceflight-general signature is anchored by immune-activation and inflammatory pathways and is corroborated by the Mars-500 analog. The Twins Study lymphocyte changes cluster with the spaceflight-general signature. The support is real but partial: the oxidative-stress and epigenetic-aging categories are genuinely shared, and the corpus marks them as shared rather than forcing a verdict. Triangulation across studies improves the attribution; it does not deliver the isolation that only a properly designed experiment could.

The third hypothesis held that reversibility, not the presence of a change, is the health-relevant readout, and that the literature shows a reversibility gradient. It is supported, with the caveat that the reversibility evidence is the thinnest part of the corpus. Where follow-up data exist, the spaceflight-general signature reverts preferentially and the radiation-specific signature persists preferentially; the Twins Study's own report that most flight-associated methylation reverted after return places its findings in the reversible class. The gradient is coherent and consequential, and it is also under-sampled — a finding and a gap at once.

The principal original contribution of this article is the Spaceflight–Radiation Methylation Corpus: the first cross-study catalogue that places spaceflight-reported and radiation-reported DNA methylation findings in immune cells into a single frame, cross-classified by exposure source and by post-exposure reversibility. The corpus is a resource, not a measurement. Its value is that it makes the attribution claim auditable — it replaces the assertion that radiation caused a

methylation change with the placement of that change relative to exposure-resolved evidence, and it lets any reader see which entry and which source a disputed placement rests on. To my knowledge no such resource existed; the spaceflight-omics and radiation-epigenetics literatures have run in parallel without a frame that renders them commensurable. The corpus is offered as that frame, and as a structure that the field can extend and correct as new data arrive.

Four limitations bound the conclusions, and they should be read as conditions on the contribution rather than as afterthoughts. The first is that the corpus is a synthesis of heterogeneous studies — different platforms, cell preparations, doses, and pipelines — harmonized at the level of functional locus category; the harmonization is interpretive, and a different curator might classify particular entries differently. The second is that the corpus cannot rescue the N-of-1 problem: it improves the interpretation of the Twins Study but cannot make one twin pair into a population, and the broader flown sample with methylation data remains small. The third is that the reversibility axis is sparsely populated, because many source studies did not sample long enough after exposure; the reversibility gradient is a well-grounded hypothesis, not a closed result. The fourth is that almost all the human spaceflight data in the corpus come from low Earth orbit, so the corpus indexes the deep-space galactic-cosmic-radiation environment only through its heavy-ion analog entries, and that indexing is indirect.

Three directions for future work follow. The first is observational and specific: longitudinal repetitive-element methylation should be measured in returning crews well after landing, not only during flight, because that is the measurement the corpus identifies as the cleanest index of a persistent, radiation-specific change. The second is the systematic exploitation of ground analogs: pairing isolation analogs such as Mars-500 with controlled heavy-ion irradiation studies, on matched cell types and platforms, would let the radiation-specific and isolation-driven signatures be separated far more cleanly than the present heterogeneous corpus allows. The third is the extension of the corpus itself — into other epigenetic marks beyond DNA methylation, into other immune cell subsets, and, as deep-space missions eventually generate data, into the exposure regime that low Earth orbit cannot reach.

The Twins Study will remain a landmark, and it should. But a landmark is most useful when its findings are read for exactly what they support. The astronaut's immune-cell methylation changed during his year in space; most of it changed back; and the change is best understood as the integrated epigenetic response to the spaceflight environment as a whole, not as the fingerprint of galactic cosmic radiation. The fingerprint of radiation is a fainter and more specific mark — repetitive-element hypomethylation, persisting after return — and finding it will take the measurements the corpus was built to specify.

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EPIGENETSKE MODIFIKACIJE DNK METILACIJE U LIMFOCITIMA IZLOŽENIM GALAKTIČKOM KOSMIČKOM ZRAČENJU: STUDIJA NA BLI- ZANCIMA U PROGRAMU NASA TWINS STUDY

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Sažetak: NASA Twins Study jedinstven je eksperiment: jedan jednojajčani blizanac proveo je godinu dana na Međunarodnoj svemirskoj stanici dok je njegov genetski identičan brat ostao na Zemlji, a poređenje između njih izolovalo je biologiju svemirskog leta od konfaunda genetske razlike. Među promjenama koje je studija dokumentovala bile su izmjene u DNK metilaciji u imunim ćelijama astronauta, u blizini gena koji upravljaju imunom funkcijom. Te su se promjene otad citiraju kao dokaz kako galaktičko kosmičko zračenje prepisuje epigenom. Ovaj članak tvrdi da citiranje nadmašuje dokaze. Twins Study ima uzorak od jednog para blizanaca, a okruženje svemirskog leta koje je uzorkovala objedinjuje galaktičko kosmičko zračenje s mikrogravitacijom, izolacijom, poremećajem spavanja, povišenim ugljen-dioksidom i izmijenjenom ishranom — pa se promjena metilacije uočena kod blizanca koji je letio ne može, prema dizajnu studije, pripisati zračenju radije nego bilo kojoj drugoj komponenti tog skupa. Uz to, Međunarodna svemirska stanica orbitira unutar zaštite Zemljine magnetosfere, gdje je doza galaktičkog kosmičkog zračenja tek dio onoga što bi posada na putu ka Marsu primila. Originalni doprinos ovog članka je Korpus Metilacije Svemirskog Leta i Zračenja — prvi međustudijski katalog diferencijalno metilisanih lokusa i funkcionalnih puteva u imunim ćelijama, sastavljen iz osamnaest SCOPUS-indeksiranih studija i unakrsno klasifikovan prema izvoru izloženosti — skupu svemirskog leta, izolovanom jonizujućem zračenju i analogu galaktičkog kosmičkog zračenja — te prema reverzibilnosti nakon izloženosti. Korpus prvi put omogućava čitanje rame uz rame: signatura specifična za zračenje, koncentrisana u lokusima odgovora na oštećenje DNK, genima oksidativnog stresa i hipometilaciji repetitivnih elemenata, djelimično je odvojiva od signature opšte za svemirski let, koncentrisane u putevima imune aktivacije i upale. Pročitane naspram korpusa, promjene metilacije limfocita iz Twins Study pretežno se preklapaju sa signaturom opštom za svemirski let, i većina ih se vratila u baznu vrijednost nakon povratka na Zemlju. Korpus preusmjerava interpretativni zadatak s detekcije promjene metilacije na njeno smještanje unutar referentnog okvira razlučenog po izvoru izloženosti i po reverzibilnosti.

Ključne riječi: *DNK metilacija, galaktičko kosmičko zračenje, limfociti, NASA Twins Study, epigenetika, atribucija izloženosti, korpus metilacije svemirskog leta i zračenja.*