OFF-LABEL NEUROIMAGING*

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The growth of neuroimaging evidence in the courtroom is consistent with the increased reliance on technical and machine-based specialties at trial. Litigants routinely seek to introduce neuroimaging evidence in both civil and criminal trials to supplement traditional medical, psychiatric, and psychological opinion testimony. A substantial portion of neuroimaging evidence is still in the developmental stage—what I term "off-label neuroimaging." Unsurprisingly, evaluating the reliability of developing neuroimaging poses challenging questions for gatekeeping courts. Among the complex evidentiary issues neuroimaging presents for courts and litigants, this Article considers one foundational question: How should courts determine whether neuroimaging evidence is sufficiently reliable for trial?

To help courts evaluate the reliability requirements for developing neuroimaging evidence, this Article examines what I term "off-label neuroimaging" in two ways: (1) medical neuroimaging not yet clinically adopted; and (2) neuroimaging for which there is no proof of ecological validity, or "real world" use. This Article explains the shortcomings of off-label neuroimaging and proposes a framework to guide the courts, providing an explanation of why simply applying the Daubert factors is often insufficient to manage the problems the evidence poses. For medical neuroimaging used diagnostically, the proposed framework suggests that courts give greater weight to the consensus position of medical practice in determining whether evidence is both foundationally reliable and reliable as applied. Additionally, for non-medical (such as fMRI lie detection), the Article urges courts to apply the ecological validity test that considers whether the evidence has been tested in the "real world."

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INTRODUCTION

Science and technology provide much of the evidence introduced at trial, including machine-driven specialties such as gas chromatography, DNA comparisons, electronic data, and GPS cell service location evidence.[1] Given the growing preference for machine evidence over human assessment,[2] it is not surprising that litigants seek to introduce neuroimaging evidence in both civil and criminal trials to supplement traditional psychiatric or psychological opinion testimony.[3] With the growing reliance on neuroimaging in both criminal and civil cases, complex questions arise in determining its admissibility.

This Article considers one foundational question: How should courts determine whether neuroimaging evidence is sufficiently reliable for trial? Three examples showcase the problem: First, Diffusion Tensor Imaging

1. For an in-depth explanation, see generally Andrea Roth, *Machine Testimony*, 126 YALE L.J. 1972 (2017) (discussing the rise of machine testimony in court and offering a coherent framework for conceptualizing and regulating such evidence).

2. *Id.* at 1975 (noting that the "past century has witnessed a noteworthy rise in the 'silent testimony' of instruments") (quoting MIRJAN R. DAMAŠKA, EVIDENCE LAW ADRIFT 143 (1997)).

3. For a sample of neuroimaging admitted in a wide variety of cases, see, for example, *United States v. Hinckley*, 672 F.2d 115 (D.C. Cir. 1982) (admitting neuroimaging in an insanity defense case), *Graham v. Florida*, 560 U.S. 48, 68 (2010) (recognizing the importance of neuroimaging data in a criminal case involving juveniles and noting that "developments in psychology and brain science continue to show fundamental differences between juvenile and adult minds"), *Dickson v. United Airlines, Inc.*, No. 4:20-CV-5014-RMP, 2021 WL 4199954, at *3 (E.D. Wash. Aug. 3, 2021) (ruling that multiple forms of structural and functional neuroimaging were sufficiently reliable to be admitted at trial as proof of traumatic brain injury (TBI)), *Baltes v. Metro. Life Ins. Co.*, No. 2:23-cv-07404-MRA-JPR, 2025 WL 319946, at *12 (C.D. Cal. Nov. 12, 2025) (finding plaintiff's expert credible and her reliance on Single Photon Emission Computed Tomography (SPECT) scans was appropriate objective proof that the claimant's brain was "injured and poorly functioning." Thus, plaintiff qualified for long term disability), *United States v. Henderson*, 2022 WL 4931753, at *1 (W.D. Mo. 2022) (admitting neuroimaging evidence of vascular infarct and atherosclerotic disease resulting in chronic neurological impairment; court held that defendant was incompetent to stand trial), and *Row v. Miller*, 591 F. Supp. 3d 778, 874–75 (D. Idaho 2021) (failure to present evidence of brain atrophy as mitigation in a capital case was ineffective assistance of counsel).

("DTI"), used in research science,[4] is often admitted into the courtroom as proof of traumatic brain injury ("TBI")[5] even though it is not yet adopted for diagnostic purposes in clinical practice.[6] Second, Positron Emission Tomography ("PET scan"), used medically to evaluate brain tumors and neurodegenerative disorders such as Alzheimer's and Parkinson's disease,[7] is often admitted in criminal cases as an explanation for diminished criminal responsibility,[8] although there is little agreement about whether that use is reliable. Third, litigants have sought to introduce functional magnetic resonance imaging ("fMRI") as proof of a defendant's truth-telling, despite no "real world" proof that fMRI is, in fact, capable of lie detection.

These determinations that courts make are complex and difficult. They must determine whether the evidence is sufficiently reliable under Federal Rule of Evidence 702[9] (or correlative state rules of evidence) and consistent with the *Daubert* factors—challenging tasks.[10] First, the court must find that the proponent has established the "foundational reliability" of the evidence by a preponderance. That is, the evidence must be based upon sufficient facts and data and be the product of both reliable principles and methods.[11] Second, the judge must also determine whether the expert has reliably applied such

4. *See infra* Part III.

5. *See, e.g.*, *infra* Part III.

6. *See* Jennifer Christine van Velkinburg, Mark D. Herbst & Stewart M. Casper, *Diffusion Tensor Imaging in the Courtroom: Distinction Between Scientific Specificity and Legally Admissible Evidence*, 11 WORLD J. CLIN. CASES 4477, 4480–87 (2023).

7. MEHDI DJEKIDEL, DAWOOD TAFTI & JOE M. DAS, NUCLEAR MEDICINE NEURO PET ASSESSMENT, PROTOCOLS, AND INTERPRETATION 3–4 (2025).

8. *See* Deborah W. Denno, *The Myth of the Double-Edged Sword: An Empirical Study of Neuroscience Evidence in Criminal Cases*, 56 B.C. L. REV. 493, 495–97, 548 (2015). This Article does not discuss the reliability of PET scan evidence, as it was considered in an earlier article, Jane Campbell Moriarty, Daniel D. Langleben & James M. Provenzale, *Brain Trauma, PET Scans, and Forensic Complexity*, 31 BEHAV. SCI. & L. 702 (2013).

9. Federal Rule of Evidence 702, Testimony by Expert Witnesses, provides:

> A witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if the proponent demonstrates to the court that it is more likely than not that: (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue; (b) the testimony is based on sufficient facts or data; (c) the testimony is the product of reliable principles and methods; and (d) the expert's opinion reflects a reliable application of the principles and methods to the facts of the case.

FED. R. EVID. 702.

10. Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579, 593–95 (1993) (listing factors relevant to proof of reliability, including testability, error rate, peer review and publication, existence of standards and methods, and general acceptance).

11. In 2023, Federal Rule of Evidence 702 was amended and "clarifies that the preponderance standard applies to the three reliability-based requirements [702(b), (c), and (d)] added in 2000 . . . ." FED. R. EVID. 702 advisory committee's note to 2023 Amendment.

principles and methods to the facts of the case.[12] These requirements are not just for cross-examination but are essential findings prior to admissibility.[13] As noted in the Advisory Committee Notes to the 2023 Amendment to Rule 702, "[M]any courts have held that the critical questions of the sufficiency of an expert's basis, and the application of the expert's methodology, are questions of weight and not admissibility. These rulings are an incorrect application of Rules 702 and 104(a)."[14]

To help courts apply the reliability requirements for neuroimaging evidence, this Article examines what I term "off-label neuroimaging" in two ways: (1) medical neuroimaging not yet clinically adopted; and (2) non-medical imaging for which there is no proof of ecological validity, or "real world" use.[15] This Article explains the shortcomings of off-label neuroimaging and proposes a framework to guide the courts, providing an explanation of why simply applying the *Daubert* factors is often insufficient to manage the problems of neuroimaging evidence. For medical neuroimaging used diagnostically, the proposed framework suggests that courts give greater weight to the consensus position of medical practice in determining whether evidence is both foundationally reliable and reliable as applied. Additionally, for neuroimaging evidence that has no medical application (such as fMRI lie detection), the Article urges courts to apply the ecological validity test that considers whether the evidence has been tested in the "real world."

The Article proceeds as follows. Part I introduces the problem and provides a short explanation of neuroimaging modalities commonly offered in court. Part II explains the medical use of the off-label concept and applies it to neuroimaging evidence, using DTI research on TBIs as a case-in-point. It also uses fMRI lie detection to explain the need for ecological validity. Part III explains the evidentiary problems that off-label neuroimaging poses and proposes a framework for courts.

I. NEUROIMAGING EVIDENCE[16]

Courts evaluating advanced neuroimaging techniques often struggle to understand the technology, its limitations, and whether it is scientifically

12. "Rule 702(d) has also been amended to emphasize that each expert opinion must stay within the bounds of what can be concluded from a reliable application of the expert's basis and methodology." *Id.*

13. *Id.*

14. *Id.*

15. There is some overlap in these categories, but as the Article explains, the primary distinction is between medically based neuroimaging used diagnostically (such as DTI or PET) and imaging that is primarily used in research, such as fMRI.

16. For a more complete discussion on neuroimaging evidence by this author, see generally Jane Campbell Moriarty, *Neuroimaging Evidence in US Courts*, *in* LAW AND MIND: A SURVEY OF LAW AND

reliable. Neuroimaging evidence presents concerns about complex areas of overlapping expertise,[17] issues of small, underpowered research studies,[18] the interplay between research data and clinical adoption,[19] and the problem of applying group data to an individual.[20] Simultaneously, some neuroimaging poses questions about "ecological validity,"[21] or what courts refer to as "real world testing."[22]

While the term "neuroscience" generally refers to the scientific study of the nervous system, it also encompasses diverse fields of study from physics to basic biology.[23] During the last several decades, technology has developed rapidly in the neuroscience fields, propelled by the ability to create images of the brain, often explained as "structural" and "functional" imaging: the former is focused on anatomical structures and the latter is concerned with changes concurrent with a cognitive or behavioral task.[24] Examples of neuroimaging relevant to courtroom evidence are x-rays, computed tomography scans ("CT scans"), magnetic resonance imaging ("MRI"), PET scan, single photon emission computed tomography ("SPECT"), electroencephalography ("EEG"), the quantitative EEG ("QEEG"),[25] DTI, and fMRI.

THE COGNITIVE SCIENCES (Bartosz Brożek, Francis X. Shen, Nicole A Vincent & Jaap Hage eds., Cambridge Univ. Press, 2021) (providing an overview of neuroimaging technologies and their use in United States courts). This discussion of neuroimaging technology borrows from that chapter.

17. For a detailed discussion of this issue, see Jane Campbell Moriarty & Daniel D. Langleben, *Who Speaks for Neuroscience? Neuroimaging Evidence and Courtroom Expertise*, 68 CASE W. RSRV. L. REV. 783, 785–91 (2018).

18. *See* Katherine S. Button, John P.A. Ioannidis, Claire Mokrysz, Brian A. Nosek, Jonathan Flint, Emma S.J. Robinson & Marcus R. Munafò, *Power Failure: Why Small Sample Size Undermines the Reliability of Neuroscience*, 14 NAT. REV. NEUROSCIENCE 365, 365 (2013).

19. *See infra* Part I.

20. C.C. Meltzer, G. Sze, K.S. Rommelfanger, K. Kinlaw, J.D. Banja & P.R. Wolpe, *Guidelines for the Ethical Use of Neuroimages in Medical Testimony: Report of a Multidisciplinary Consensus Conference*, 35 AM. J. NEURORADIOLOGY 632, 633–34 (2014).

21. *See* Yana Suchy, Libby A DesRuisseaux, Michelle Gereau Mora, Stacey Lipio Brothers & Madison A Niermeyer, *Conceptualization of the Term "Ecological Validity" in Neuropsychological Research on Executive Function Assessment: A Systematic Review and Call to Action*, 30 J. INT. NEUROPSYCHOLOGICAL SOC. 499, 505–18 (2024).

22. United States v. Semrau, 693 F.3d 510, 521–23 (6th Cir. 2012) (upholding the trial court's decision to exclude neuroimaging testing about lie detection and discussing the problems of "real world testing" of the technology).

23. Boris Kotchoubey, Felix Tretter, Hans A. Braun, Thomas Buchheim, Andreas Draguhn, Thomas Fuchs, Felix Hasler, Heiner Hastedt, Thilo Hinterberger, Georg Northoff, Ingo Rentschler, Stephan Schleim, Stephan Sellmaier, Ludger Tebartz Van Elst & Wolfgang Tschacher, *Methodological Problems on the Way to Integrative Human Neuroscience*, at 2, *in* 10 FRONTIERS IN INTEGRATIVE NEUROSCIENCE art. 41 (2016), https://doi.org/10.3389/fnint.2016.00041 [https://perma.cc/38V3-CZLM (staff-uploaded archive)].

24. Moriarty & Langleben, *supra* note 17, at 786 (providing a more in-depth explanation of this distinction).

25. EEG and QEEG represent graphs of electrical activity in the brain and are often included under the term "neuroimaging evidence," but this Article does not describe them in further detail.

Structural imaging includes x-rays, CT scans, and MRIs. In the trauma setting, x-rays (formally, "radiography") may be used to diagnose skull fractures, for example, but are less useful to image other injuries to the brain. CT scans also use x-rays, but also create a three-dimensional rendering that is often the first choice for traumatic injuries, strokes, intracranial hemorrhages, and other emergency conditions.[26] MRI employs strong magnetic fields and non-ionizing electromagnetic radiation to produce high-resolution images,[27] and its development has had an "unparalleled importance" both for diagnostic medicine and for research[28] and is used, for example, to image brain tumors and track brain lesions over time.[29] DTI depicts the white matter in the brain and is used for research on various disorders and diseases. It is also used to image TBI ("mTBI"), which are difficult to image with standard imaging techniques. DTI depicts the brain's white matter mapping by measuring the displacement of water molecules using diffusion anisotropy,[30] creating three-dimensional pictures of the organization of axonal fiber bundles in the brain.[31] Because DTI measures the "direction and magnitude of water diffusion, it enables the visualization of neural pathways and connectivity, making it an indispensable tool for understanding brain anatomy, function, and pathology."[32] While CT and MRI have well-accepted uses in medicine, DTI is not yet adopted in clinical practice except for presurgical planning.[33]

X-ray evidence has been admitted for more than a century, consistent with its accepted role in clinical medicine.[34] For decades, courts have recognized that CT scans and MRIs, in line with their use in clinical medicine, can provide evidence of injuries (for example, skull fractures or serious head trauma),

26. For a detailed discussion, see Erin D. Bigler, Mark Allen & Gary K. Stimac, *MRI and Functional MRI*, at 27–40, *in* NEUROIMAGING IN FORENSIC PSYCHIATRY: FROM THE CLINIC TO THE COURTROOM (J.R. Simpson ed. 2012) [hereinafter NEUROIMAGING].

27. Daniel D. Langleben, Dan F.X. Willard & Jane C. Moriarty, *Brain Imaging of Deception*, *in* NEUROIMAGING, *supra* note 26, at 217.

28. Nikos K. Logothetis, *What We Can Do and What We Cannot Do with fMRI*, 453 NATURE 869, 869 (2008).

29. Bigler et al., *supra* note 26, at 27.

30. Yaniv Assaf & Ofer Pasternak, *Diffusion Tensor Imaging (DTI)-based White Matter Mapping in Brain Research: A Review*, 34 J. OF MOLECULAR NEUROSCIENCE 51, 51 (2008). For an interesting and influential article about the origins of mapping water diffusion in the brain, see generally Denis Le Bihan, *Diffusion MRI: What Water Tells Us About the Brain*, 6 EMBO MOLECULAR MED. 569 (2014). For a contemporary explanation of DTI, see Logan Ranzenberger, Joe M. Das & Travis Snyder, *Diffusion Tensor Imaging*, NCBI (2023), https://www.ncbi.nlm.nih.gov/books/NBK537361/ [https://perma.cc/74BB-QDSX].

31. Le Bihan, *supra* note 30, at 569.

32. Ranzenberger et al., *supra* note 30, at 1.

33. Matthew Grant, JiaJing Liu, Max Wintermark, Ulas Bagci & David Douglas, *Current State of Diffusion—Weighted Imaging and Diffusion Tensor Imaging for Traumatic Brain Injury Prognostication*, 33 NEUROIMAGING CLINICS N. AM. 279, 281 (2023).

34. An early reported case in 1918 admitted x-ray evidence as proof of a skull fracture. *See* United Laundries Co. v. Bradford, 105 A. 303 (Md. 1918).

medical conditions (for example, hemorrhages, traumatic brain injury, strokes, and damage from toxins), and certain disease processes (for example, tumors, Alzheimer's disease).[35]

Functional imaging techniques are designed to show activation in the brain—rather than just structure—and include PET, SPECT, and fMRI.[36] fMRI was developed in the early 1990s and has had a phenomenal impact on basic cognitive research.[37] Although researchers employ fMRI to generate thousands of studies, its clinical utility has not fully been realized. Research using fMRI has potential clinically relevant uses for psychiatry, for example, but progress has been slower than anticipated and hoped.[38] To date, fMRI has been used in presurgical brain mapping, generally for resection of tumors and in epilepsy surgery.[39] fMRI has not been introduced in court with the notable exception of unsuccessful attempts as lie detection evidence.[40]

PET and SPECT are functional neuroimaging modalities within nuclear medicine that measure brain function based on the uptake of biological molecules, such as glucose, that have a chemical link to isotopes. The presence or absence of these isotopes in the brain can then be imaged and are used for detecting the histological grade of brain tumors, diagnosing Parkinson's disease, and locating seizures' foci.[41] Despite the many clinical indications for PET and SPECT, their use as evidence of traumatic brain injury, mental illness, or damage due to toxic exposure is not well established.[42]

Some researchers use PET and SPECT to find neurological function that would explain abnormal behavior,[43] and both neurologists and psychologists

35. For example, physicians routinely use structural imaging, generally CT and sometimes MRI, to diagnose individuals with suspected traumatic brain injury. *See* Robert P. Granacher, *Traumatic Brain Injury*, *in* NEUROIMAGING, *supra* note 26, at 43, 46. MRI has been used clinically since the 1980s. *See* Logothetis, *supra* note 28, at 869.

36. Scientists are also using diffusion MRI ("DMRI"), which measures the rate of water diffusion as modulated by brain activity, to investigate neuronal activation. Le Bihan, *supra* note 30, at 572.

37. Logothetis, *supra* note 28, at 896.

38. *See* Helen S. Mayberg, *Neuroimaging and Psychiatry: The Long Road from Bench to Bedside*, 44 HASTING CTR. REP. S31–S36 (2014) (explaining how clinical applications of functional neuroimaging are arriving quite slowly, particularly in psychiatry).

39. *See, e.g.*, Michael A. Silva et al., *Challenges and Techniques for Presurgical Brain Mapping with Functional MRI*, 17 NEUROIMAGING CLIN. 794, 794 (2018) ("[c]urrently, fMRI is the most commonly used non-invasive neuroimaging modality for surgical planning . . .").

40. *See, e.g.*, United States v. Semrau, 693 F.3d 510, 523 (6th Cir. 2012).

41. Susan E. Rushing, Daniel A. Pryma & Daniel D. Langleben, *PET and SPECT in* NEUROIMAGING IN FORENSIC PSYCHIATRY: FROM THE CLINIC TO THE COURTROOM 8 (Joseph R. Simpson eds., 2012); Moriarty, *supra* note 8, at 704.

42. Moriarty, *supra* note 8, at 704.

43. *See, e.g.*, Adrian Raine, Monte Buchsbaum & Lori LaCasse, *Brain Abnormalities in Murderers Indicated by Positron Emission Tomography*, 42 BIOLOGICAL PSYCH. 495, 496–97 (1997).

have offered PET and SPECT testimony in cases involving violent behavior.[44] As noted by scholars collecting and analyzing empirical data, PET and other forms of functional neuroimaging have been and continue to be admitted in both the guilt and penalty phase, sentencing, of criminal trials.[45] However, in the courtroom, experts testify about neuroimaging modalities in ways that are not adopted by consensus medical opinion.

II. OFF-LABEL MEDICINE

In the United States, the Federal Drug Administration ("FDA") regulates the sale and marketing of pharmaceutical products and requires proof that a new medication is safe and effective at a given dose.[46] FDA approval is an expensive and lengthy process for pharmaceutical companies, often costing several billion dollars and taking a decade or more from beginning to end.[47] As a result of the length and expense of bringing a new drug to market, the manufacturer often promotes the drug's use for a medical indication (i.e., a disease), in a population (e.g., pediatric patients), or in a dosage different from that approved by the FDA.[48] This off-label use "involves prescribing medications for indications, or using a dosage or dosage form, that have not been approved" by the FDA,[49] although the practice is both legal and common.[50] Off-label use occurs where given populations such as children, pregnant women, and individuals with mental health disorders were not included in the original trials. It also is used compassionately for life-threatening or terminal conditions.[51] And finally, off-

44. *See, e.g.*, Ruben C. Gur, Oren M. Gur, Arona E. Gur & Alon G. Gur, *A Perspective on The Potential Role of Neuroscience in The Court*, 85 FORDHAM L. REV. 547, 547 (2016) (explaining Ruben Gur's role as a consultant and expert in death penalty cases).

45. *See, e.g.*, Denno, *supra* note 8, at 545; Henry T. Greely & Nita A. Farahany, *Neuroscience and the Criminal Justice System*, 2 ANN. REV. CRIMINOLOGY 451 *passim* (2019).

46. Elizabeth Richardson, *Off-Label Drug Promotion*, HEALTH AFFAIRS (June 30, 2016), https://www.healthaffairs.org/content/briefs/off-label-drug-promotion [https://perma.cc/6BWU-XLTK]; *see also* Katharine A. Van Tassel, *New Drug Applications: The Importance of the Process*, *in* 1 FOOD & DRUG ADMIN. § 13.1 (2025) (providing an in-depth explanation of the process).

47. JAMES T. O'REILLY & KATHARINE A. VAN TASSEL, FOOD AND DRUG ADMINISTRATION § 13.1 (4th ed., 2025-1).

48. Chrisopher M. Wittich, Cristopher M. Burkle & William L. Lanier, *Ten Common Questions (and Their Answers) About Off-label Drug Use*, 87 MAYO CLINIC PROC. 982, 982 (2012). Some of this use is driven by the pharmaceutical companies. *See* Gail A. Van Norman, *Off-Label Use vs. Off-Label Marketing of Drugs*, 8 J. AM. COLL. CARDIOLOGY: BASIC TO TRANSLATIONAL SCI. 224, 224 (2023) ("Motivated to increase sales and prescriptions . . . manufacturing companies frequently encourage expanded use through marketing activities . . .").

49. Wittich, et al., *supra* note 48, at 982; Van Norman, *supra* note 48, at 225.

50. Randall S. Stafford, *Regulating Off-Label Drug Use—Rethinking the Role of the FDA*, 358 NEJM 1427, 1427 (2008); Rebecca Dresser & Joel Frader, *Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, 37 J. MED. ETHICS 473, 476–77 (2010) (describing the process of FDA approval for a product and its approved indications for use, and noting that physicians may legally prescribe such drugs for uses not covered by the approved label).

51. *See* Wittich, et al., *supra* note 48, at 983.

label medicines are prescribed where studies or guidelines suggest a beneficial use for a specific illness.[52]

Off-label prescribing is common in virtually all specialties, presenting many advantages and some clear drawbacks.[53] For example, the Covid-19 pandemic highlighted the benefits and risks of the vaccine for populations that had not been included in the original study.[54] The pandemic also led to off-label prescribing of experimental treatments for the virus.[55] During the early days of the pandemic, lay people and some health professionals began promoting the use of chloroquine and hydroxychloroquine to ease symptoms, without proof from practice or "rigorous research studies" that the medications were efficacious for treating suspected or confirmed infection.[56] Despite the fact that serious side effects could occur from the administration of these drugs, they continued to be offered in clinical settings in the United States and elsewhere.[57]

The general growth of off-label prescribing concerns medical, ethical, and legal professionals due to the medications' uncertain efficacy and their risks of side effects.[58] By some estimates, more than 20% of commonly prescribed medications are for an off-label indication.[59] The practice is "extremely common worldwide,"[60] and often without adequate supporting scientific data.[61] One study stated "73% of off-label mentions had little or no scientific support."[62]

52. Shariful A. Syed, Brigham A. Dixon, Eduardo Constantino & Judith Regan, *The Law and Practice of Off-Label Prescribing and Physician Promotion*, 49 J. AM. ACAD. PSYCHIATRY & L. 53, 53 (2021).

53. *Id.* at 53.

54. *See, e.g.*, Jennifer E. DeSante Berktau, Timothy K. Knilans, Govind Persad, Patricia J. Zettler, Holly Fernandez Lynch & Arman H. Mathey Antommaria, *Off-Label Prescription of Covid-19 Vaccines in Children: Clinical Ethical, and Legal Issues*, 149 PEDIATRICS 1, 1 (2022).

55. Syed et al., *supra* note 52, at 53; Jennifer S. Bard, *The President's Remedy—What the Hydroxychloroquine Story Teaches Us About the Need to Limit Off-Label Prescribing*, 71 CATH. U. L. REV. 427, 430–41 (2022).

56. Syed et al., *supra* note 52, at 53.

57. *Id.* (noting that both chloroquine and hydroxychloroquine could cause rare and serious side effects); Bard, *supra* note 55 (providing an in-depth explanation of this specific example of off-label use and off-label prescribing as a whole).

58. *See* Bard, *supra* note 55, at 451–52; Syed et al., *supra* note 52, at 53.

59. *See* David C. Radley, Stan N. Finkelstein & Randall S. Stafford, *Off-Label Prescribing Among Office-Based Physicians*, 166 ARCH. INTERN. MED. 1021, 1024 tbls. 1 & 2 (2006); Bard, *supra* note 55, at 449 (citing studies that state "as many as 30% of all prescriptions are off-label"); Van Norman, *supra* note 48, at 225 (citing studies finding that off-label prescriptions account for "21% to 32.3% of prescriptions overall").

60. Sandeep Kumar Gupta & Roopa Prasad Nayak, *Off-Label Use of Medicine: Perspective of Physicians, Patients, Pharmaceutical Companies and Regulatory Authorities*, 5 J. PHARMACOLOGY & PHARMACOTHERAPEUTICS 88, 88–89 (2014).

61. *See* Radley et al., *supra* note 59, at 1025; Bard, *supra* note 55, at 451–52.

62. Katlein França & Sergio Litewka, *Controversies in Off-Label Prescriptions in Dermatology: The Perspective of the Patient, the Physician, and the Pharmaceutical Companies*, 58 INT'L J. DERMATOLOLOGY 788, 789 (2019).

A few examples provide helpful illustration of the concerns off-label prescribing poses. Gabapentin, approved in 1993 for seizure disorders and epilepsy and later for post-herpetic neuralgia,[63] is a prime example of a drug used far more off-label than on-label. It is now commonly prescribed for neuropathic pain, neuropathy, psychiatric disorders, and sleep-movement disorders.[64] In a 2018 study, authors noted that up to 95% of gabapentin is prescribed for off-label indications, often for treating pain so as to avoid prescribing opioids.[65] By 2024, gabapentin was the fifth most dispensed drug in the United States,[66] and often given to older adults.[67] Unfortunately, gabapentin's safety has been questioned when combined with opioids or benzodiazepines, as it presents risks of increased respiratory depression and substance-related overdoses.[68] Physicians often prescribe gabapentin to individuals over sixty-five,[69] a group prone to falling. Indeed, falling is the leading cause of injury related death for that population.[70] Given the dangers of gabapentin-induced "dizziness, somnolence, gait disturbance, and potential for misuse,"[71] there are significant risks associated with its use in an older population.

So too, the drug ketamine, first developed in the 1970s, was not approved by the FDA for any mental health disorder, but is now used off-label for

63. *See* Kristjan Linnet, Bjarni Pall Linnet Runolfsson, Johann Agust Sigurdsson & Larus Steinthor Gudmundsson, *Incident Gabapentin Prescribing Associated with Opioid and Benzodiazepine/Z-Drug Prescribing: A Population-Based Longitudinal Study in Primary Care*, at 2, *in* 16 FRONTIER PHARMACOLOGY (2025), https://doi.org/10.3389/fphar.2025.1583415 [https://perma.cc/9LHX-CWMJ (staff-uploaded archive)].

64. *See* Gupta & Nayak, *supra* note 60, at 90; *see also* Joseph I. Sirven, *New Uses for Older Drugs: The Tales of Aspirin, Thalidomide, and Gabapentin*, 85 MAYO CLINIC PROC. 508, 509 (2010), https://pubmed.ncbi.nlm.nih.gov/20511480/ [https://perma.cc/U8RK-765N] (noting that gabapentin is also used off-label to treat "premenstrual syndrome, migraine headache, and drug and alcohol withdrawal seizures").

65. *See* Alyssa M. Peckham, Kirk E. Evoy, Leslie Ochs & Jordan R. Covvey, *Gabapentin for Off-Label Use: Evidence-Based or Cause for Concern?*, 12 SUBSTANCE ABUSE: RSCH. & TREATMENT 1, 1 (2018), https://doi.org/10.1177/1178221818801311 [https://perma.cc/VNQ5-LY6M (staff-uploaded archive)].

66. *See* Andrea E. Strahan, S. Michaela Rikard, Kristine Schmit, Kun Zhang & Gery P. Guy Jr., *Trends in Dispensed Gabapentin Prescriptions in the United States, 2010 to 2024*, 178 ANNALS INTERN. MED. 1186, 1186 (2025).

67. *See id.*

68. *See* Linnett et al., *supra* note 63, at 2.

69. *See* Strahan et al., *supra* note 66, at 1816.

70. *See Older Adult Falls Data*, CDC: HEALTH TOPICS (Oct. 28, 2024), https://www.cdc.gov/falls/data-research/index.html [https://perma.cc/GZS8-4THW].

71. Strahan et al., *supra* note 66, at 1816.

depression.[72] The untimely death of actor Matthew Perry illuminated the off-label and sometimes illegal surge of ketamine use[73] in the United States.[74]

Both ketamine and gabapentin highlight some of the dangers of off-label prescribing. However, multiple beneficial uses exist for the practice, such as late-stage cancer treatments, new therapies in mental health treatment, and pain relief for children—populations generally not included in the original studies.[75] At the same time, the safety of these drugs may be inadequately studied in these vulnerable populations who are often excluded from clinical research.[76]

While off-label prescribing is largely unregulated in the practice of medicine, there are suggested FDA guidelines about communications from manufacturing firms to health care providers.[77] The FDA suggests (as it does not regulate the practice of medicine) that physicians are free to use pharmaceuticals provided there is firm scientific rationale and sound medical evidence for its use.[78] There are suggested frameworks for using off-label pharmaceuticals and medical devices,[79] but practitioners must use their professional judgment,[80] and much off-label prescribing is done in the absence of supporting data.[81] As there is "virtually no oversight of off-label drug or

72. *See* Paul Nagele, Charles R. Conway & Charles F. Zorumski, *Purposeful Drug Repurposing*, 82 JAMA PSYCHIATRY 638, 638 (2025), https://jamanetwork.com/journals/jamapsychiatry/article-abstract/2833556 [https://perma.cc/NGR9-9R98 (staff-uploaded archive)].

73. *See* Matt Stevens & Chris Hamby, *Matthew Perry's Death Shines a Harsh Light on Ketamine Treatment*, N.Y. TIMES (Aug. 19, 2024), https://www.nytimes.com/2024/08/19/arts/television/matthew-perry-ketamine-treatment.html?searchResultPosition=9 [https://perma.cc/27BH-AMJ9 (staff-uploaded, dark archive)]; *Real Stories of Using Ketamine for Depression, Anxiety, PTSD*, ADDITUDE, https://www.additudemag.com/ketamine-treatment-for-depression-mood-disorders/ [https://perma.cc/A5VD-4866 (staff-uploaded archive)] (last updated May 9, 2025).

74. From 2017 to 2022, there was a 5.5-fold increase in the use of patients prescribed ketamine and the proportion of individuals with a billing diagnosis of depression increased from 5.3% to 28.3% in that period. *See* Brian S. Barnett, Roger D. Weiss & Gerard Sanacora, *Strengthening Safeguards for Psychiatric Uses of Ketamine*, 82 JAMA PSYCHIATRY 333, 333 (2025), https://jamanetwork.com/journals/jamapsychiatry/article-abstract/2829808 [https://perma.cc/8PYQ-EULB (staff-uploaded archive)].

75. *See* Wittich et al., *supra* note 48, at 983.

76. *See* Van Norman, *supra* note 48, at 226.

77. *See* Bard, *supra* note 55, at 465; *see, e.g.*, U.S. FOOD & DRUG ADMIN., COMMUNICATIONS FROM FIRMS TO HEALTH CARE PROVIDERS REGARDING SCIENTIFIC INFORMATION ON UNAPPROVED USES OF APPROVED/CLEARED MEDICAL PRODUCTS: QUESTIONS AND ANSWERS (2025).

78. *See* Van Norman, *supra* note 48, at 225.

79. *See* Emily A. Largent, Franklin G. Miller & Steven D. Pearson, *Going Off-label Without Venturing Off-Course, Evidence and Ethical Off-label Prescribing*, 169 ARCH. INTERN. MED. 1745, 1745–46 (2009), https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/724320 [https://perma.cc/GJ9S-WPSY (staff-uploaded archive)].

80. *See* Madlen Gazarian, Maria Kelly, John R. McPhee, Linda V. Graudins, Robyn L. Ward & Terence J. Campbell, *Off-Label Use of Medicines: Consensus Recommendations for Evaluating Appropriateness*, 185 MED. J. AUSTL. 544, 544 (2006), https://doi.org/10.5694/j.1326-5377.2006.tb00689.x [https://perma.cc/L7M3-SQKG (staff-uploaded archive)].

81. *See* Stafford, *supra* note 50, at 1427.

device use," problems are often noticed only when there are whistleblowers or when a sufficient number of patients are harmed.[82] To address the concerns that off-label use poses, much consideration is given to both sound medical evidence and the consensus of the medical profession—ideas worth borrowing for courtroom evaluation of neuroimaging evidence.[83]

III. OFF-LABEL NEUROIMAGING

During the last decade, the legal and medical communities have attempted to create consensus guidelines for neuroimaging testimony and address concerns about how such evidence is being used at trial.[84] Nonetheless, some experts testify in ways that contravene neuroimaging's accepted uses.[85] Judges, as the gatekeepers of evidence, are often without much guidance about whether neuroimaging is reliable for the purposes it is being used or whether it is being used inconsistently with clinical standards. As one judge noted when evaluating DTI and declining to admit it as evidence under the *Frye* general-acceptance standard, "The march of science is inexorable. This has created a challenge for trial courts in deciding what 'scientific' evidence is truly worthy of the name. How is a Judge, a presumed expert in jurisprudence, but a lay person in science, to make such a determination?"[86] Four years later, another judge in the same state ruled that DTI was admissible, finding that DTI was both reliable and an accepted diagnostic tool within the scientific community, citing testimony from an expert witness that the "White Paper," the consensus opinion of the American College of Radiology Head Injury Institute, was not a scientific paper but was "used for marketing."[87]

Given the complexity of the problem and the condensed time in which courts must learn and evaluate scientific evidence in a given case, off-label

82. *Id.* at 226 (discussing the Fen-Phen dangers and subsequent lawsuits).

83. *See, e.g.*, Gazarian et al., *supra* note 80, at 545–47; Largent et al., *supra* note 79, at 1745–46.

84. *See, e.g.*, C.C. Meltzer, G. Zse, K.S. Rommelfander, K. Kinlaw, J.D. Banja & P.R. Wolpe, *Guidelines for the Ethical Use of Neuroimages in Medical Testimony: Report of a Multidisciplinary Consensus Conference*, 35 AM. J. NEURORADIOLOGY 632, 632–33 (2014); Max Wintermark, Pina C. Sanelli, Yoshimi Anzai, A. John Tsioursis & Christopher Whitlow, *Imaging Evidence and Recommendations for Traumatic Brain Injury: Conventional Neuroimaging Techniques*, 12 J. AM. COLL. RADIOLOGY e1, e2 (2015), http://dx.doi.org/10.1016/j.jacr.2014.10.014 [https://perma.cc/GGK3-2RXS (staff-uploaded archive)].The latter article was endorsed by the ACR Head Injury Institute, the American Society of Neuroradiology, the American Society of Functional Neuroradiology, and the American Society of Pediatric Neuroradiology. *See, e.g.*, AM. COLL. RADIOLOGY, ACR APPROPRIATENESS CRITERIA: HEAD TRAUMA (2020), https://acsearch.acr.org/docs/69481/Narrative/ [https://perma.cc/FRH7-H4DS].

85. *See*, *e.g.*, United States v. Semrau, 693 F.3d 510, 516–17 (6th Cir. 2012).

86. Brouard v. Convery, 59 Misc. 3d 233, 235, 70 N.Y.S.3d 820, 821 (2018) (recognizing the existing consensus papers on the subject and determining that "DTI technology is not generally accepted . . . in the field of neurology for use in the clinical treatment of individual patients").

87. Lee v. Troge, No. 50958/18, 2022 WL 534342, at *3 (N.Y. Sup. Ct. Feb. 22, 2022) (unpublished table decision).

neuroimaging poses a challenging evidentiary problem[88] that might benefit from courts' understanding of and deference to medicine's consensus guidelines for advanced imaging.

For clinically recognized neuroimaging, the task of evaluating neuroimaging evidence is straightforward, as the imaging is used in medical practice for agreed-upon purposes, has been approved by the FDA, and is listed as appropriate for these purposes by the American College of Radiology Appropriateness Criteria. For example, the ACR Appropriateness Criteria ("ACRAAC") for Head Trauma pairs the type of concern (e.g., head trauma)[89] with the appropriate (and "not usually appropriate") forms of imaging (e.g., acute head trauma, mild ("GCS 13-15").[90] Notably, the website also lists studies related to the subject (e.g., head trauma).[91] This link includes the ranked quality of the study, listed as a number from one (highest) through four (lowest) or a meta-analysis. Significantly, the ACRAAC also includes neuroimaging modalities that are not clinically used or approved, which is a focus on this Article.

A. *Medical Imaging Before Clinical Adoption*

Although DTI is not yet adopted for clinical practice and is not listed as appropriate imaging for TBI by the American College of Radiology,[92] some experts are testifying that it can be used to diagnose TBI and even mTBI. TBI is a substantial health concern in both the United States and throughout the world as a result of accidents, crimes, falls, sport-related injuries, attempted suicide, and blast-related and penetrating brain injury in military and civilian settings.[93] In the United States, Center for Disease Control and Prevention data suggest that 1.7 million people are affected annually by TBI, and nearly

88. Professor Edward Cheng explains that the task facing most judges managing scientific evidence is to learn and evaluate complicated and competing views on scientific evidence when there is "scarcely enough time for lay decisionmakers to acquire a surface-level understanding of the material, let alone develop the expertise necessary to make informed judgments." Edward K. Cheng, *The Consensus Rule: A New Approach to Scientific Evidence*, 75 VAND. L. REV. 407, 416 (2022). This observation is certainly true for neuroimaging evidence.

89. *See ACR AC Portal*, AM. COLL. OF RADIOLOGY, https://gravitas.acr.org/ACPortal/Index [https://perma.cc/AJW3-Z4PX].

90. *See Appropriateness Criteria: Head Trauma—Evidence*, AM. COLL. OF RADIOLOGY, https://acsearch.acr.org/list/GetEvidence?TopicId=139&TopicName=Head%20Trauma [https://perma.cc/NV8F-XGDB].

91. *See ACR AC Portal* , *supra* note 89.

92. *See id.*

93. Grant et al., *supra* note 33, at 279–80 (citing MARK FAUL, MARLENA M. WALD, LIKANG XU & VICTOR G. CORONADO, U.S. DEP'T OF HEALTH & HUM. SERVS., CTRS. FOR DISEASE CONTROL & PREVENTION, NAT'L CTR. FOR INJURY PREVENTION & CONTROL, TRAUMATIC BRAIN INJURY IN THE UNITED STATES: EMERGENCY DEPARTMENT VISITS, HOSPITALIZATIONS AND DEATHS 2002–06 (2010)); *see also* Jane Campbell Moriarty, Daniel D. Langleben & James M. Provenzale, *Brain Trauma, PET Scans and Forensic Complexity*, 31 BEHAV. SCI. & L. 702, 702–08 (2013).

3 million people are living with long term disability from TBI. Head injuries are classified as mild, moderate, or severe, and mTBI presents specific problems with its reporting and imaging.[94] mTBI is underreported, lacks a universally accepted diagnosis, and is difficult to image with either CT or MRI imaging, which are standard hospital imaging techniques for head trauma assessment.[95] Additionally, between 10–20% of individuals with mTBI have persistent symptoms, which are believed to be a result of shearing forces that lead to "impaired microstructural integrity or diffuse axonal injury" in the brain.[96] Yet proving such injuries has been elusive.

After 2000, researchers began using DTI to image white matter in the brain[97] and for research on TBI, particularly mTBI, which is difficult to image with standard imaging techniques. DTI images the white matter mapping of the brain by measuring the displacement of water molecules using diffusion anisotropy.[98] This imaging creates three-dimensional pictures of the organization of axonal fiber bundles in the brain.[99] Researchers believe DTI is particularly promising for imaging axonal damage following mTBI, and a 2025 review of seventy-nine studies supports "an association between changes in DTI parameters and acute mTBI." However, there are substantial areas of contention.[100] DTI is still in the investigatory phase and a 2025 review of these seventy-nine studies suggests only its "cautious integration into the clinical assessment of mTBI."[101] This large review, however, noted the numerous current concerns that the DTI presents for imaging mTBI and counsels that "[e]stablishing consensus guidelines for performing DTI analysis in mTBI research may help mitigate discrepancies and allow for more meaningful comparisons between studies."[102] Moreover, the review suggests developing "consensus-driven guidelines" for the research that "emphasize the importance

94. Shiv Patil, Mert Karabacak, Serhat Aydin, Inna Sagi, Andrea Soddu, Burak Berksu Ozkara, Konstantinos Margetis & Sotirios Bisdas, *Diffusion Tensor Imaging in Acute, Chronic, and Remote Mild Traumatic Brain Injury: A Systemic Review of Cross-Sectional and Longitudinal Studies*, 42 J. NEUROTRAUMA 1671, 1671–72 (2025).

95. *Id.* at 1672.

96. *Id.*

97. For a detailed explanation of DTI, see Lauren J. O'Donnell & Carl-Fredrik Westin, *An Introduction to Diffusion Tensor Image Analysis*, 22 NEUROSURGERY CLINICS OF N. AM. 185 (2011), https://doi.org/10.1016/j.nec.2010.12.004 [https://perma.cc/4J2V-ZCPE (staff-uploaded archive)].

98. Yaniv Assaf & Ofer Pasternak, *Diffusion Tensor Imaging (DTI)-based White Matter Mapping in Brain Research: A Review*, 34 J. OF MOLECULAR NEUROSCIENCE 51, 51–52 (2008). For an interesting and influential article about the origins of mapping water diffusion in the brain, see Denis Le Bihan, *Diffusion MRI: What Water Tells Us About the Brain*, 6 EMBO MOLECULAR MED. 569, 569 (2014).

99. Le Bihan, *supra* note 98, at 569. For an excellent explanation of DTI and why it does not meet the *Frye, Daubert*, or Rule 702 tests, see Andrew Lehmkuhl, *Diffusion Tensor Imaging: Failing Daubert and Fed. R. Evid. 702 in Traumatic Brain Injury Litigation*, 87 U. CIN. L. REV. 279, 285 (2018).

100. Patil et al., *supra* note 94, at 1687.

101. *Id.* at 1671.

102. *Id.* at 1690.

of longitudinal studies with single-subject analysis that could promote the validity and unique application of this technique."[103] Thus, the research is promising and with "[m]ulticenter collaborations and large scale studies with harmonized methodologies" to validate DTI, it will be "a reliable tool for both research and clinical applications in mTBI."[104] Another recent journal article agrees that research looks "promising" but highlights the current limitations in the studies.[105] These authors note two aspects of the current research that should concern us for trial evidence: the DTI data for TBI patients can only be established at the group level, and the exact cutoff for normal versus abnormal has not been established—both of which are prerequisites for establishing foundational reliability in the courtroom.[106]

As with much neuroimaging research, the data generated and published has problems of "study heterogeneity"—studies differ in the patient populations, the locations of injuries, timing, imaging protocol, brain regions examined, and so on.[107] Additionally, there is no true "normative" database with normal control subjects and standardized clinical and research neuroimaging protocols, which causes problems in distinguishing normal from abnormal.[108] Critically, the technique has not yet made the shift from research to clinical use.[109] As the authors conclude, "Advanced imaging and image analysis techniques, coupled with the development of a normative database to conduct both traditional and machine learning-based research, will be needed to translate this technique from the lab to the clinic."[110]

Medical neuroimaging that has not transitioned "from the lab to the clinic" cannot meet the standard of foundational reliability in the courtroom. Yet, despite these serious concerns, some experts testify that DTI is sufficiently reliable for the courtroom as proof of TBI. For example, in *Marsh v. Celebrity Cruises*,[111] the district court ruled that DTI was reliable under a *Daubert* analysis, noting there were nearly 3,500 papers on DTI in peer review journals and 83 of them involved DTI to image TBI.[112] The court stated that the error rate was no different than MRI and that as the expert in question estimated a 1–2% error in

103. *Id.*

104. *Id.*

105. Grant et al., *supra* note 33, at 286–88. For a helpful explanation of the issues, the various consensus positions, and the appropriate and ethical uses of advanced neuroimaging for mTBI, see Hal S. Wortzel, *Advanced Neuroimaging and Mild Traumatic Brain Injury Litigation, Revisited*, 50 J. AM. ACAD. PSYCHIATRY L. 336, 338–39 (2022).

106. Grant et al., *supra* note 33, at 279.

107. *Id.* at 288.

108. *Id.* at 289–90.

109. *Id.* at 290. For an extensive explanation of the shortcomings of DTI, see Lehmkuhl, *supra* note 99, at 290–94 (explaining the multiple reasons why DTI is not currently reliable).

110. Grant et al., *supra* note 33, at 292.

111. No. 1:17-cv-21097, 2017 WL 6987718 (S.D. Fla. Dec. 15, 2017).

112. *Id.* 2017 WL 6987718, at *3–4.

his interpretation, the court said there was a "98% certainty error free rate" in the witness's opinion.[113] While there is much to criticize in the opinion, it has influenced other courts. For example, in *Canyes v. Carnival Corp.*,[114] the district court adopted the *Daubert* analysis of *Marsh*, finding it "persuasive on its own terms," as it considered DTI under the Eleventh Circuit's three-part test to determine whether expert testimony should be admitted under *Daubert*.[115] Specifically, *Marsh* ruled that DTI was a generally accepted method for analyzing and diagnosing TBI, had been peer-reviewed extensively, had a documented rate of error, and "[s]ince 2022 DTI has increasingly gained acceptance by courts."[116] In a helpful article explaining the scientific problems of DTI as legal evidence, Andrew Lehmkuhl analyzes cases between 2005 and 2017, concluding that "DTI is overwhelmingly being admitted into evidence," despite its substantial shortcomings.[117] His statement that "*Daubert* is not serving its purpose in practice," is a position with which many would agree with off-label neuroimaging and other forms of expert evidence generally.[118]

An essential problem with the *Daubert* factors is that they do not equate with reliability when all the studies are small, most of them are not replicated, and the methods of conducting the studies vary by researcher. The studies may be well done, but they do not establish foundational reliability given the concerns articulated above. Not surprisingly, courts may not appreciate the implications of these shortcomings but the concerns are critical to the proper evaluation of the evidence.

B. *Non-Medical Imaging*

Scientists have generated a wealth of neuroimaging data in multiple fields, including behavioral science, economics, and even lie detection, using fMRI technology.[119] However, fMRI research has substantial limits: the studies are small; the research is infrequently replicated; and data is often generated for a group, rather than for single-subjects. Additionally, the technology requires

113. *Id.* at *4.

114. 700 F. Supp. 3d 1102 (S.D. Fla. 2023).

115. *Id.* at 1124.

116. DAVID L. FAIGMAN, EDWARD K. CHENG, ERIN E. MURPHY, JOSEPH SANDERS & CHRISTOPHER SLOBOGIN, MODERN SCIENTIFIC EVIDENCE: THE LAW & SCIENCE OF EXPERT TESTIMONY § 20:4 (2025–26 ed.) (collecting cases).

117. Lehmkuhl, *supra* note 99, at 298.

118. *Id.* at 300. *See also* Cheng, *supra* note 88 (explaining *Daubert*'s multiple shortcomings).

119. *See* Geoffrey K. Aguirre, *Functional Neuroimaging: Technical, Logical, and Social Perspectives*, 45 HASTINGS CTR. REP. S8, S8–18 (2014).

compliant subjects who must follow instructions[120]—not always possible in research designed for courtroom use.

fMRI generates data from a small number of participants (usually less than thirty), and often with less data per person than is needed.[121] According to one meta-analysis, the commonly used task fMRI measures generally do not have the test-retest reliability necessary for biomarker discovery or brain-behavior mapping.[122] The weight of commentary suggests that neuroscience studies are too small, underpowered, and infrequently replicated to be conclusive.[123] As in other areas of scientific research,[124] this lack of replication generates concern about the reliability of these studies.[125] As commentators explain, even determining which hypothesis to attempt to replicate in brain imaging is challenging, as many experiments lack the power to find the "sought-after differences in neural activity due to limitations in the reliability of measures combined with cost considerations limiting sample sizes."[126]

There are several attempts currently in progress to address these concerns,[127] but these problems are common in scientific research and not likely to be resolved quickly. However, unlike other complex expert evidence that is relevant in the courtroom, such as DNA comparisons, the claimed reliability of some neuroimaging is premised solely upon these small, underpowered, nonreplicated studies.

The use of fMRI technology for lie detection was at issue in the seminal case of *United States v. Semrau*,[128] where the defendant sought to introduce expert evidence of an fMRI lie detection test as proof that the defendant was being truthful in his responses to questions relevant to the indictment.[129]

120. *See* Maxwell L. Elliott, Annchen R Knodt, David Ireland, Meriwether L Morris, Richie Poulton, Sandhya Ramrakha, Maria L Sison, Terrie E Moffitt, Avshalom Caspi & Ahmad R Hariri, *What Is the Test-Retest Reliability of Common Task-Functional MRI Measures? New Empirical Evidence and a Meta-Analysis*, 31 PSYCH. SCI. 792, 803, 804 (2020).

121. *See id.* at 804. *But see* Phillip A. Kragel, Xiaochen Han & Tor D. Wagner, *Functional MRI Can Be Highly Reliable, but It Depends on What You Measure: A Commentary on Elliott et al.*, 32 PSYCH. SCI., 622, 622–24 (2021) (referencing the study in Elliott et al.).

123. *See* Elliott et al., *supra* note 120, at 803; *see* Button, *supra* note 18, at 365.

124. *See generally* Jane Campbell Moriarty, Daniel D. Langleben & James M. Provenzale, *Brain Trauma, PET Scans and Forensic Complexity*, 31 BEHAV. SCI. & L. 702 (2013) (discussing that many courts "admit PET scan evidence without much critical analysis").

125. *See* Robert E. Kelly, Jr. & Matthew J. Hoptman, *Replicability in Brain Imaging*, at 2, *in* 12 BRAIN SCI. 1 (2022), https://www.mdpi.com/2076-3425/12/3/397 [https://perma.cc/9S9M-NBPS]; Rotem Botvinik-Nezer & Tor D. Wagner, *Reproducibility in Neuroimaging Analysis: Challenges and Solutions*, 8 BIOLOGICAL PSYCH.: COGNITIVE NEUROSCIENCE & NEUROIMAGING 780, 782–83 (2023).

126. Kelly & Hoptman, *supra* note 125, at 2.

127. *See, e.g.*, *id.* at 1–2 (citing and discussing studies).

128. 693 F.3d 510 (6th Cir. 2012)

129. *See id.* at 516–24 (discussing the problems of "real world testing" that fMRI lie detection posed and how that failure undergirded the Magistrate Judge's decision to exclude the testimony).

Among the multiple shortcomings the evidence presented, the court was troubled by the unproven accuracy of the studies "in the real world." Despite lab-produced data claiming to distinguish truth from lies, there was no evidence that fMRI lie detection worked in the real world where lying had consequences.[130] Researchers often use the term "ecological validity" to determine whether research data generated can "predict a real-world functional outcome."[131] With fMRI lie detection, the Court of Appeals for the Sixth Circuit affirmed the finding of the district court, determining that such data could not predict such an outcome.[132]

The problem of ecological validity is squarely at issue in the courtroom use of fMRI lie detection. There are dozens of fMRI studies evaluating whether it can be used to distinguish deceptive answers from truthful ones; the data suggest that fMRI may be able to eventually make this distinction, if large scale trials to prove its accuracy.[133] One study compared polygraph with fMRI lie detection and concluded that "fMRI was significantly more likely to detect deception than polygraphy."[134] But as the authors note, "*[T]he jury remains out on whether fMRI will become a forensic tool*."[135] In other words, its ecological validity was not yet established.

Thus, for nonmedical use of neuroimaging (such as fMRI lie detection), proof of foundational reliability requires proof that it possesses ecological validity. To date, the courts have rejected fMRI lie detection because, in part, there is no proof of its efficacy in the real world. Thus, the concept of ecological validity is one that meshes with proof of foundational reliability and reliability as applied.

IV. THE COURTS' DILEMMA AND PROPOSED FRAMEWORK

In evaluating the admissibility of expert evidence, Judges are required in most courts to evaluate the foundational reliability of the evidence and the reliability of the evidence as applied. They make this evaluation considering the

130. *See id.* at 513–24.

131. *See* Suchy et al., *supra* note 21, at 502 (discussing multiple definitions of the term "ecological validity" and noting that this definition was prevalent and arguing for more standardization with the term "criterion validity").

132. *Semrau*, 693 F.3d at 531.

133. *See* Daniel D. Langleben & Jane Campbell Moriarty, *Using Brain Imaging for Lie Detection: Where Science, Law, and Policy Collide*, 19 PSYCH., PUB. POL'Y & L. 222, 239 (2013) (arguing that the probability of detecting liars in a cohort of both liars and truthtellers requires more ecologically valid testing and a larger overall number of participants to create a large-scale trial).

134. Daniel D. Langleben, Jonathan G. Hakun, David Seelig, An-Li Wang, Kosha Ruparel, Warren B. Bilker & Ruben C. Gur, *Polygraphy and Functional Magnetic Resonance Imaging in Lie Detection: A Controlled Blind Comparison Using the Concealed Information Test*, 77 J. CLINICAL PSYCH. 1372, 1377, 1379 (2016).

135. *Id.* at 1379 (emphasis added).

"liberal thrust" of the Federal Rules of Evidence[136] and the belief that "[v]igorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence."[137] Judges may conflate credentials with reliability, particularly when these experts are conducting research at elite universities or run clinics treating individuals with head injuries, for example. And critically, most judges do not have—nor should they be expected to have—the background or time to fully understand the complexity these forms of evidence present.

Trial judges are meant to be generalists, deciding what is sufficiently reliable across fields. In making these determinations, judges must distinguish reliable evidence from that based on "*fausse*" expertise or "junky" science.[138] Since the *Daubert* decision in 1993,[139] courts around the country have been making these decisions on a variety of subjects that range from flawed forensic science such as bitemarks to complicated questions of medical causation in toxic torts. In his concurring/dissenting opinion in *Daubert*, Justice Rehnquist explained that twenty-two amicus briefs filed in the case did not provide legal or policy arguments but "definitions of scientific knowledge, scientific method, scientific validity, and peer review—in short, matters far afield from the expertise of judges."[140] A similar point was made by the Court of Appeals on remand in *Daubert*, seeming to imply that the Supreme Court was demanding more from judges than reasonably could be delivered:

> As we read the Supreme Court's teaching in *Daubert*, therefore, though we are largely untrained in science and certainly no match for any of the witnesses whose testimony we are reviewing, it is our responsibility to determine whether those experts' proposed testimony amounts to "scientific knowledge," constitutes "good science," and was "derived by the scientific method." Mindful of our position in the hierarchy . . . , we take a deep breath and proceed with the heady task.[141]

The jurists' comments are relevant to neuroimaging evidence, which has complex areas of expertise, underpowered research studies, technology not yet

136. *See* Beech Aircraft Corp. v. Rainey, 488 U.S. 153, 169 (1988); Daubert v. Merrell Dow Pharms., Inc., 509 U.S 579, 596 (1993).

137. *Id.*

138. Kumho Tire Co. v. Carmichael, 526 U.S. 137, 159 (1999) (Scalia, J., concurring) (remarking that the district court has "discretion to choose among *reasonable means* of excluding expertise that is *fausse* and science that is junky").

139. *Daubert*, 509 U.S. 579 (1993).

140. *Id.* at 599 (Rehnquist, J., concurring in part and dissenting in part).

141. Daubert v. Merrell Dow Pharms., Inc., 43 F.3d 1311, 1316 (9th Cir. 1995).

clinically adopted, and group data applied diagnostically to an individual.[142] How can we expect judges to tease apart and resolve the problems to determine reliability in an area where there are so many existing issues to be addressed within the research itself?

Judges grappling with the complexity of scientific and nonscientific expert evidence is an incredibly labor-intensive task. Nearly every substantial civil case includes a *Daubert* challenge, as United States District Court Judge Patti Saris noted at a conference on Federal Rule of Evidence 702.[143] Given the cognitive load for judges to understand areas far from their areas of expertise, it is not surprising that many courts often default to following the lead of other courts in admitting evidence after one or a few courts provide an analysis of its reliability.[144] Moreover, courts "must decide cases in finite time, with limited resources, and often based only on the information presented by the parties."[145]

Professor Edward Cheng notes that judges (and juries) do not really understand much of the expert testimony presented, and asks: "If judges are not experts, how can they effectively gatekeep?"[146] Professor Cheng suggests "scrapping" *Daubert* and looking to the consensus of the scientific community when it exists, a position that he believes is more epistemically defensible, reflects a better understanding of science, and avoids the problems created by *Daubert*.[147] His compelling article has generated much discussion,[148] and he provides an elegant conceptual proposal for the role of consensus opinion when juries evaluate evidence at trial. Professor Cheng's prospective suggestion for scientific evidence critiques the current Daubert regime and focuses largely on the jury's role.

142. For a detailed discussion of the problem of group-to-individual inference in scientific evidence generally, see David L. Faigman, John Monahan & Christopher Slobogin, *Group to Individual (G2i) Inference in Scientific Expert Testimony*, 81 U. CHI. L. REV. 417, 421–26 (2014). The article suggests the use of "best practices" and well-accepted protocols in evaluating error rates. *Id.* at 455–57 (citing Arnold J. Rosoff, *Evidence-Based Medicine and the Law: The Courts Confront Clinical Practice Guidelines*, 26 J. HEALTH POL. POL'Y & L. 327, 343 (2001)) (noting that the medical profession has established protocols for conducting tests, including brain scans).

143. *See* The Honorable Patti B. Saris, Chief Judge of the U.S. Dist. Ct. for the Dist. of Mass., *Remarks at the Fordham Law Review Symposium on Forensic Expert Testimony, Daubert, and Rule 702 (Oct. 27, 2017)*, 86 FORDHAM L. REV. 1463, 1536 (2018).

144. Jane Campbell Moriarty, *Deceptively Simple: Framing, Intuition, and Judicial Gatekeeping of Forensic Feature-Comparison Methods Evidence*, 86 FORDHAM L. REV. 1687, 1701–03 (2018).

145. Cheng, *supra* note 88, at 431.

146. *Id.* at 410.

147. *See id.* at 435–48 (explaining his views). This article focuses on a single subject—neuroimaging evidence—and provides a framework for judges *currently* addressing questions of admissibility and reliability. By comparison, Professor Cheng's proposal suggestions a prospective approach for scientific evidence that focuses largely on the jury's role and the questions it answers.

148. *See, e.g.*, *2022 Villanova Law Review* Norman J. Shachoy Symposium: *The Consensus Rule: A New Approach to Admissibility of Scientific Evidence*, 67 VILL. L. REV. 837 (2022).

For now, however, judges must still decide how to evaluate developing neuroimaging evidence and whether it meets mandated reliability requirements. With diagnostic neuroimaging, consensus must be from the field of medicine, not from research scientists or individual physicians.[149] Judges cannot and should not be expected to parse the details of research disagreements where there is yet no clinical adoption of the imaging for the purposes used in court. Such evidence is not only "off label" but *contrary* to the consensus of the medical profession.

This Article thus proposes two approaches to help the courts: The first relates to medical neuroimaging evidence used diagnostically in an individual, either as primary or supporting evidence.[150] Testimony from a physician[151]must provide proof of medical consensus that the given technology is appropriate for the purpose for which it is being offered in court.[152] The proponent of the evidence would be burdened to establish, by a preponderance, why such consensus positions should not govern their use in the courtroom.[153]

Second, for other forms of non-medical neuroimaging *not* used diagnostically (such as fMRI lie detection), the proponent must establish its ecological validity to meet the burden of foundational reliability. The proponent must show such imaging works in the real world.

There are, of course, competing arguments to this proposal. The first one, to use a metaphor, is that this ship has sailed. In other words, large waves of neuroimaging evidence (like DTI) have come into courts around the country. While that might be factually correct, it is insufficient. Law, science, and evidence must all evolve to ensure greater accuracy. We have witnessed the

149. Professor Cheng's resolution seeks a "trans-substantive reform that only defers to consensus when it exists and relates to a factual issue . . . with a rule of inference . . . if the relevant scientific community believes a fact involving specialized knowledge, then that fact is established accordingly." Cheng, *supra* note 88, at 436.

150. The distinction between an expert testifying that a brain scan is proof of injury versus "consistent with" injury may not be terribly meaningful. Offering evidence as supporting proof or claiming only that it is "consistent with an injury" should not relieve the proponent of the obligation to prove its reliability. Historically, misleading communication in forensic science evidence has been often plagued with the problem of using terms like "consistent with." The evidence is either reliable, or it is not. For an explanation of the problem of potentially misleading communication in forensic identification evidence, see Dawn McQuiston-Surrett & Michael J. Saks, *Communicating Opinion Evidence in the Forensic Identification Sciences: Accuracy and Impact*, 59 HASTINGS L.J. 1159, 1161–62, 1169–71 (2008).

151. Moriarty & Langleben, *supra* note 17, at 802–03.

152. *See ACR AC Portal*, *supra* note 89

153. The 2023 amendment to Rule 702 and the accompanying Advisory Committee Notes clarify that the proponent of the evidence must meet the requirements of the rule by a preponderance of the evidence, pursuant to the Rule 104(a) standard. As the notes emphasize, an expert's opinions must "stay within the bounds of what can be concluded from a reliable application of the expert's basis and methodology." FED. R. EVID. 702 advisory committee's note to 2023 amendment.

trend of forensic evidence improving for just this reason. Neuroimaging should be no different.

A stronger argument in favor of admitting such evidence is essentially that "perfection is the enemy of the good"—neuroimaging evidence is still better than the current psychiatric and psychological evidence often admitted or that DTI may be the best neuroimaging evidence to date for supporting proof of mTBI. As explained by Professor Deborah Denno, "[t]he capacity of imaging to provide a scientific assessment—however imperfect—of the brain's condition is a much-needed improvement over previous reliance upon a profession whose experts espoused primarily their own opinions."[154] Professor Denno's argument is compelling and worthy of consideration, particularly in criminal cases where the defendant's life or liberty is at issue.

Professor Denno is not alone in this argument. Judge Easterbrook relied on similar reasoning in *United States v. Bonds*[155] when addressing the substantial false positive rate of fingerprint analysis.[156] "What are the alternatives," he asks, comparing fingerprints to lying witnesses, poor eyewitness identification, and grainy bank surveillance photos. Instead, he would leave this to cross-examination and whether the witness took steps to reduce error.[157] Fingerprints, even if flawed, are better than other forms of problematic evidence.

These arguments make intuitive sense, but I still believe that proof of reliability is what separates science from other endeavors. As DTI research continues to develop, it may well be the best evidence of mTBI. But currently, DTI is not at that point, and we should not give it a pass because it is "more scientific" than other forms of evidence we rely upon in court. We have historically made this error throughout history with expert testimony on witchcraft, visual hair comparison, blue-light evidence, forensic odontology, and bullet lead comparison. All were thought to be scientifically valid at the time; all were found to be terribly flawed.

The current state of the law requires more. As the advisory committee notes to the 2023 amended Rule 702 explain, "the preponderance standard applies to the three reliability-based requirements added in 2000—requirements that many courts have incorrectly determined to be governed by the more permissive Rule 104(b) standard."[158] The questions of foundational reliability and reliability as applied are not simply for cross-examination. The reason for these requirements is sensible: to avoid unreliable evidence from

154. Deborah W. Denno, *Neuroscientific Evidence in Context*, *in* LAW AND MIND: A SURVEY OF LAW AND THE COGNITIVE SCI. 412, 416 (Bartosz Brozek, Jaap Hagge & Nicole A Vincent, eds. 2021). particularly in criminal cases where the defendant's life or liberty is at issue.

155. 922 F.3d 343 (7th Cir. 2019).

156. *Id.* at 346.

157. *Id.*

158. FED. R. EVID. 702 advisory committee's note to 2023 amendment.

becoming admitted and entrenched in courtrooms as it has in the past. For neuroimaging evidence, foundational reliability requires consensus medical evidence and proof from the real world.

CONCLUSION

Modern advances in neuroimaging are worth celebrating. But the law must recognize the substantial risks inherent in allowing neuroimaging evidence into court without a clear understanding of its potential unreliability. As the science and medical fields continue to develop and refine these technologies, the courts should wait until they are ready for use in the real world. There has long been a debate about the relationship and timing of science and law; neuroimaging technologies are one more aspect of that long-existing conversation. For developing neuroimaging technologies, we should require consensus evidence and proof of real-world efficacy.