No. 22-1716

UNITED STATES COURT OF APPEALS
FOR THE FIRST CIRCUIT

JERRY CINTRON,
Plaintiff-Appellee,

v.

PAUL BIBEAULT, in his official and individual capacity; RUI DINIZ, in his official and individual capacity; MATTHEW KETTLE, in his official and individual capacity; PATRICIA ANNE COYNE-FAGUE, in her individual capacity; WAYNE T. SALISBURY JR., Interim Director, in his official capacity; SPECIAL INVESTIGATOR STEVE CABRAL, in his official and individual capacity; JEFFREY ACETO, in his individual and official capacity; LYNNE CORRY, in her individual and official capacity,
Defendants-Appellants,

LT. HAYES, in his official and individual capacity; LT. MOE, in his official and individual capacity; LT. BUSH, in his official and individual capacity; JENNIFER CHAPMAN, in her official and individual capacity; "COUNSELOR" FRANCO, in her official and individual capacity,
Defendants.

On Appeal from the U.S. District Court for the District of Rhode Island
Case No. 1:19-cv-497; Chief Judge John J. McConnell

BRIEF OF AMICUS CURIAE CENTER FOR LAW, BRAIN & BEHAVIOR IN SUPPORT OF PLAINTIFF-APPELLEE

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United Nations Mandela Rules, National Commission on Correctional Healthcare, American Psychological Association, Office of Justice Programs, DOJ 2

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CORPORATE DISCLOSURE STATEMENT

Pursuant to Federal Rule of Appellate Procedure 26.1, the *amici curiae* state that none has had a corporate parent, none issues stock, and no publicly held corporation owns 10% or more of any of them, individually or collectively.

IDENTITY AND INTEREST OF AMICI CURIAE CENTER FOR LAW, BRAIN & BEHAVIOR

The mission of the Center for Law, Brain & Behavior (CLBB) at Massachusetts General Hospital is to put the most accurate and actionable neuroscience in the hands of people who shape the standards and practices of the legal system and affect its impact on people's lives. By equipping system actors in this way, CLBB works to make the legal system more effective and more just. CLBB provides expert training, tools, and counsel to help members of the legal community understand and apply the most relevant brain science to cases, courtroom procedures, and policies. Amicus is uniquely positioned to provide this Court with the scientific community's current understanding of the brain, as related to solitary confinement.

SUMMARY OF THE ARGUMENT

For over a century, scientists have studied the destructive psychological and physical effects of solitary confinement.[1] The consensus is clear: Extreme conditions of isolation – like those experienced by Mr. Cintron - result in a distinctive set of emotional, social, cognitive and physical pathologies.[2] The list of

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[1] Appelbaum, KL, *American Psychiatry Should Join the Call to Abolish Solitary Confinement*, 43 J.Am.Acad. Psychiatry & the Law 2015, 43(4): 406-415, Grassian S, *Psychiatric Effects of Solitary Confinement*, 22 Wash. U. J. L. & Pol'y, 325-383 (2006).

[2] Cloud, D.H. et al, *Public Health and Solitary Confinement in the United States*, Am. J. Pub. Health 2015, 105 (1): 18-26.

adverse psychological effects is long, including impaired cognition, anxiety, panic, depression, perceptual distortions, paranoia, hallucinations, self-harm and suicide.[3] Scientists have identified the neural correlates of these known severe and persistent illnesses. Solitary confinement not only leads to enduring mental injuries, but also debilitating and persistent structural and functional brain changes. It is no surprise that solitary confinement has been universally condemned by the scientific and medical community.[4]

The tragic impact of these pathologies is illustrated by the plaintiff's assertions in this case. According to the amended complaint, before his solitary confinement, the petitioner had adjusted to his medium security facility, which allowed him extensive time out of his cell, contact with family, educational programming, and recreational and religious opportunities. In contrast, shortly after being placed in extreme isolation, with attendant sleep deprivation and stress, he developed severe anxiety, depression, perceptual disturbances and intrusive thoughts. These worsened over time, progressing to serious self-inflicted harm and extreme weight loss. Worse, Mr. Cintron's preexisting substance use disorder –

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[3] Shalev, S, *A Sourcebook on Solitary Confinement*,
SSRN: https://ssrn.com/abstract=2177495
[4] United Nations Mandela Rules, National Commission on Correctional Healthcare, American Psychological Association, Office of Justice Programs, DOJ.

known to prison authorities - was exacerbated by his segregation, as is typical for those with documented mental illness prior to solitary confinement.[5]

Mr. Cintron repeatedly informed prison personnel of his deteriorating mental and physical state; according to his complaint, even if he had not complained, his deterioration was obvious. The facility refused medication assisted substance use treatment or placement in a less restrictive environment.

The infliction of lasting damage to brain, mind, and body which Mr. Cintron's extended solitary confinement engendered was cruel – nearly two years of confinement, a profound substance abuse disorder, deepening mental and physical illness. Indeed, in Mr. Cintron's case, it was quite literally torture.

ARGUMENT

I. SOLITARY CONFINEMENT INFLICTS SEVERE AND LONG-TERM NEUROLOGICAL HARM UPON PRISONERS

A. Impact of Prolonged Isolation and Chronic Emotional Stress

Inmates in solitary confinement – like Mr. Cintron – are subject to restrictions on visits from friends and family, as well as restricted interaction with other prisoners and prison staff.[6] There is no communication with guards, no social

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[5] Stinneford, JF. *Experimental Punishments*, 2019. Notre Dame L. Rev. 95(1), 39-86; Scharff-Smith, P. *The Effects of Solitary Confinement on Prison Inmates: A Brief History and Review of the Literature*, Crime & Just. 2006, 34 (1), 441-528 (2006)

[6] Arrigo BA & Bullock, J.L., *The Psychological Effects of Solitary Confinement on Prisoners in Supermax Units: Reviewing What We Know and Recommending What*

group, no ties to the outside, no television, no phone, no windows. This extreme social isolation puts the brain and body at grave risk of isolation-mediated injuries ranging from impairment of heart health and sleep quality to brain shrinkage and cognitive decline.

Loneliness is tied to physical shrinkage in the brain. It is correlated with decreased volume of the posterior superior temporal sulcus (pSTS), an area implicated in social cognition. It has been tied to reduced gray matter (largely composed of the cell bodies of neurons) in the pSTS.[7] One study related extended social isolation to lower hippocampal volumes, an especially plastic area of the brain, core to learning and memory.[8] The volume of an individual's amygdala, central to emotional processing, reflects the size and complexity of their social networks across the lifespan; as a social network is restricted, the amygdala shrinks.[9]

Should Change, 2008, Int'l J. Offender Therapy & Comp. Criminology. 52(6), 622-640.

[7] Kanai R, et al., *Brain Structure Links Loneliness to Social Perception*, Curr. Biol. 2012, 22 (20): 1975-1979; Sandra Düzel et al., *Structural Brain Correlates of Loneliness among Older Adults*, 2019, Sci. Rep. 9: 13569.

[8] Alexander Choukèr, *Stress Challenges and Immunity in Space: From Mechanisms to Monitoring and Preventive Strategies* (2019); Niccolò Zovetti et al., *Neuroimaging Studies Exploring the Neural Basis of Social Isolation*, Epidemiology & Psychiatric Sci. 2021, 30(e29), 1-7.

[9] Kevin C. Bickart et al., *Amygdala Volume and Social Network Size in Humans*, Nat Neuroscience 2011, 14(2) 163-165; Kwak. S et al., *Social Brain Volume Is*

Social isolation not only changes brain anatomy, it can also create disordered brain function. Prolonged isolation in conditions of confinement is associated with broad reductions in global brain activity.[10] Higher loneliness scores were associated with (i) decreased blood flow from the dorsal to the ventral attentional network, and (ii) decreased flow from the emotional to the visual network; indeed, brain alterations in lonely subjects are so significant that neuroscientists can accurately predict subjective loneliness in subjects only by looking at objective altered brain activity.[11]

Evidence from evolutionary psychology and neuroscience indicates that extended social isolation causes psychologically painful chronic stress signaling.[12] For social animals, being socially excluded was evolutionarily often equivalent to

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Associated with in-Degree Social Network Size among Older Adults, 2018, Proc. Royal Soc'y B. 285.

[10] A. Jacubowski et al., *The Impact of Long-Term Confinement and Exercise on Central and Peripheral Stress Markers*, 2015, Physiology & Behav. 152 (Pt A) 106 -111; Jan Weber et al., *Neurophysiological, Neuropsychological, and Cognitive Effects of 30 Days of Isolation*, 2019, Exp Brain Res. 237 (6): 1563-1573.

[11] Yin Tian et al., *Causal Interactions in Resting-State Networks Predict Perceived Loneliness*, PLoS ONE 2017, 12 (5); Feng C. et al., *Connectome-Based Individualized Prediction of Loneliness*, 2019, Soc. Cognitive & Affective Neuroscience 14 (4), 353-365.

[12] Panksepp, J *Affective neuroscience: The foundations of human and animal emotions* (Oxford Univ. Press 1998)

death.[13] The primate neuroscience literature establishes that separation from members of social groups activates major behavioral and stress response systems.[14]

Social stressors have been shown to evoke similarly strong physiological responses in humans. Humans' extraordinary reliance on other individuals has led to the characterization of humans as the "ultra-social animal." A meta-analysis[15] showed that in humans, the threat of social exclusion stimulates the release of high levels of cortisol (and this relation was particularly strong when stress was uncontrollable).[16] Chronically high levels of cortisol are linked to increase in blood cholesterol, triglycerides, blood sugar, and blood pressure, common risk factors for heart disease, as well as increasing the likelihood of cognitive decline.[17]

Evidence links social isolation with other adverse health consequences including depression, poor sleep quality, impaired executive function, poor

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[13] Eric D. Wesselmann et al., *An Evolutionary Social Psychological Approach to Studying the Effects of Ostracism*, J. Soc., Evolutionary & Cultural Psychol. 2012, 6(3), 309-328.
[14] W. A. Mason & S. P. Mendoza, *Generic Aspects of Primate Attachments: Parents, Offspring and Mates*, 1998, 23 Psychoneuroendocrinology 23(8), 765-778.
[15] Sally S. Dickerson et al., *When the Social Self Is Threatened: Shame, Physiology, and Health*, 2004, 72 J. Personality 72, 1191-1216.
[16] Dickerson, S et al., *When the Social Self Is Threatened: Shame, Physiology, and Health*, 2004, J. Personality 72, 1191-1216.
[17] Peavy G.M. et al., *The Influence of Chronic Stress on Dementia-Related Diagnostic Change in Older Adults*, Alzheimer Disease & Associated Disord. 2012, 26(3): 260-266.

cardiovascular function and impaired immunity at every stage of life.[18] Incredibly, lack of social connection heightens health risks as much as smoking 15 cigarettes a day or having alcohol use disorder.[19] A 2019 study from the American Cancer Society, analyzing data from more than 580,000 adults, found that social isolation increases the risk of premature death from every cause for every race and, among Black participants, social isolation doubled the risk of early death while it increased the risk among white participants by 60% to 84%.[20] A study surveying more than 12,000 U.S. adults ages 50 years and older found loneliness to be associated with a 40% increase in a person's risk of dementia.[21] Two studies investigated the neurobiological correlates of loneliness and found that perceived loneliness was associated with increased amyloid and tau proteins – brain plaque aggregates commonly associated with the development of several neurocognitive diseases including dementia.[22]

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[18] Hawkley, LC & Capitanio, J.P. *Perceived Social Isolation, Evolutionary Fitness and Health Outcomes: A Lifespan Approach*, 2015, Phil. Transactions Royal Soc'y. https/doi.org/10.1098/rstb.2014.0114.
[19] Holt-Lunstad , J. et al., *Loneliness and Social Isolation as Risk Factors for Mortality: A Meta-Analytic Review*, Persp. on Psychol. Sci. 2015, 10 (2), 227-237.
[20] Alcaraz K.I. et al., *Social Isolation and Mortality in US Black and White Men and Women*, Am. J. Epidemiol 2019; 188(1):102-109.
[21] Sutin A.R. et al., *Loneliness and Risk of Dementia*, J. Gerontology B Psychol. Sci. & Soc. Sci. 2020; 75(7) : 1414-1422.
[22] Zovetti et al., *supra*; Donovan N.J., et al., *Association of Higher Cortical Amyloid Burden With Loneliness in Cognitively Normal Older Adults*, JAMA Psychiatry, 2016; 73(12): 1230-1237); D'oleire Uquillas F. et al., *Regional Tau*

Five decades of neuroscientific research suggest chronic emotional stress is neurotoxic, with stress signaling affecting brain volume in the hippocampus, amygdala and frontal cortex.[23] Physical pain and psychological pain operate via shared mechanisms in the brain.[24] With respect to chronic physical pain, neuroscientific evidence indicates that prolonged bodily pain can lead to brain atrophy.

As emotional and physical pain are processed by overlapping brain networks, chronic emotional pain, too, is associated with brain atrophy. Indeed, it is one of the strongest risk factors for the development of psychopathologies such as post-traumatic stress disorder (PTSD), as well as a robust risk factor for many medical conditions including cardiovascular disease, obesity, cancer, and immune disorders.[25] Chronic stress can manifest behaviorally as emotional numbing, concentration deficits, substance use disorders and sleep disturbances, among other

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Pathology and Loneliness in Cognitively Normal Older Adults, Translational Psychiatry 2018; 8(1), 282- 291.

[23] Lupien S.J.et al., *The Effects of Chronic Stress on the Human Brain: From Neurotoxicity, to Vulnerability, to Opportunity*, Frontiers Neuroendocrinology 2018; 49: 91-105.

[24] Macdonald G. & Mark R. Leary, *Why Does Social Exclusion Hurt? The Relationship between Social and Physical Pain*, Psychol. Bull,2005, 131(2):202-223.

[25] Macdonald & Leary, *supra*; Matosin, N. *Preclinical and Clinical Evidence of DNA Methylation Changes in Response to Trauma and Chronic Stress*, Chronic Stress 2017; DOI 10.1177/2470547017710764.

symptoms.[26] Measures of chronic emotional stress, and linked levels of chronically elevated cortisol, are correlated with shrinkage in brain volume as well as lowered connectivity in the corpus callosum and corona radiata.[27] It can cause stress-induced regression of the length of dendrites of pyramidal neurons in the hippocampus, an area of the brain critical for memory, learning, and memory formation in wake and sleep.[28]

If acute or chronic stress develops into PTSD, it can manifest as disordered network connectivity in the brain and altered brain chemistry. Patients with PTSD show smaller hippocampal and anterior cingulate volumes, hyperactive amygdala function, and diminished medial prefrontal and anterior cingulate function.[29] Patients with PTSD also show abnormally increased cortisol and norepinephrine responses to stress.[30] The medial prefrontal cortex, which exerts inhibitory control over stress responses and emotional reactivity, is reduced in volume, the degree of

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[26] Sinha, R. *Chronic Stress, Drug Use, and Vulnerability to Addiction*, Annals N.Y. Acad. of Sci. 2008; 1441(1): 105-130.
[27] Echouffo-Tcheugui, J.B.et al., *Circulating Cortisol and Cognitive and Structural Brain Measures: The Framingham Heart Study*, Neurology 2018; 91(21):1961-1970.
[28] Czéh, B et al., *Stress-Induced Changes in Cerebral Metabolites, Hippocampal Volume, and Cell Proliferation Are Prevented by Antidepressant Treatment with Tianeptine*, Proc. Nat'l Acad. Sci. U.S. Am. 2021; 98(22) 12796-12801.
[29] Kitayama, N. et al., *Smaller Volume of Anterior Cingulate Cortex in Abuse-Related Posttraumatic Stress Disorder*, J. Affective Disorders 2006; 90 (2-3) 171-174..
[30] Sutin et al., *supra*; Bremner, J.D., *Traumatic Stress: Effects on the Brain*, Dialogues Clin. Neurosci. 2006, 8(4): 445-61.

reduction associated with PTSD symptom severity.[31] The hippocampus, implicated in the control of stress responses and one of the most plastic regions in the brain,[32] atrophies in proportion to the severity of emotional trauma experienced.

These injuries are inseparable from injuries to the mind, predicting future memory impairments, inhibiting future learning and future healing.[33] Degree of cortical atrophy in stress-relevant brain regions predicts a progressive shortening of lifespan.[34]

And these effects endure. A study of more than 200,000 people released from prison found that those who had spent any time in solitary were 78% more

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[31] Rauch S.L., et al., *Selectively Reduced Regional Cortical Volumes in Post-Traumatic Stress Disorder*, 2003, Neuroreport 2003; 4(7): 913 -916; Sherin J.E. & Nemeroff, C.B., *Post-Traumatic Stress Disorder: The Neurobiological Impact of Psychological Trauma*, Dialogues Clin. Neurosci. 2011; 13(3): 263-278.
[32] Fuchs E & Gould, E., *Mini-Review: In Vivo Neurogenesis in the Adult Brain: Regulation and Functional Implications*, Euro. J. Neuroscience 2000; 12: 2211-2214.
[33] Stein M.B. et al., *Hippocampal Volume in Women Victimized by Childhood Sexual Abus*, Psychol. Med. 1997; 27(4): 951-959 ; Sapolsky, R.M, *Why Stress Is Bad for Your Brain*, Science 1996; 273 (5276): 749-750; Diamond D.M. et al, *Psychological Stress Impairs Spatial Working Memory: Relevance to Electrophysiological Studies of Hippocampal Function*, Behav. Neuroscience 1996; 110(4): 661-672.
[34] Katrinli S. et al., *Evaluating the Impact of Trauma and PTSD on Epigenetic Prediction of Lifespan and Neural Integrity*, Neuropsychopharmacology 2020;45(10): 1609-1616.

likely to die from suicide within the first year after their release than those incarcerated but not placed in solitary.[35]

B. Impact of Disrupted Sleep

The Amended Complaint alleges that the plaintiff was held in "disciplinary segregation" for a period of over a year. During that time, he spent 23 to 24 hours a day in an eight by ten room where the lights were left on all night. Throughout each night, there was a constant banging accompanying the locking of doors in his unit. Over time, such conditions contribute to the disruption of sleep and circadian cycles, potentiating both sleep-specific brain injury and disruption of normal healing effects of a natural sleep cycle. Individuals in solitary experience reduced natural light, limited artificial lighting, or constant artificial illumination.[36] Excessive exposure to light at night and limited exposure to natural light during the day can disrupt the transitions between cycles of sleep, diminish sleep quality, and decrease the amount of time one spends in essential REM sleep and deep sleep.[37]

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[35] Brinkley-Rubinstein L ,et al., *Association of Restrictive Housing During Incarceration With Mortality After Release*, JAMA Network Open 2019; 2(10).
[36] Petition for Writ of Certiorari, *Grenning v. Miller-Stout*, No. 18-9052 (2019).
[37] Wams E. J. et al., *Linking Light Exposure and Subsequent Sleep: A Field Polysomnography Study in Humans*, Sleep 2017; ;40(12): https://doi.org/10.1093/sleep/zsx165 , Münch, M et al., *Wavelength- Dependent Effects of Evening Light Exposure on Sleep Architecture and Sleep EEG Power Density in Men*, Am. J. Physiol Regul Integr Comp. Physiol. 2006; 290(5) R1421-1428.

Such sleep loss can also beget structural changes in the brain. Sleep deprivation affects concentrations of neuron-specific enolase (NSE) and S100 calcium binding protein B (S-100B) in the human brain, in one night increasing them by up to 20%. Increasing concentrations of these factors in blood reflects neuronal damage and impaired blood brain barrier function.[38] Worse sleep quality, efficiency, and daytime tiredness are related to greater hippocampal volume loss over time.[39] Regional gray matter volume of the bilateral hippocampal body is significantly correlated with sleep duration.[40] There is a clear association between sleep loss, hippocampal volume changes, and impairment of memory.[41]

Sleep loss is linked to memory pathologies ranging from mild cognitive impairment to Alzheimer's pathology. Sleep, but not wakefulness, allows removal

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[38] Benedict C.. et al., *Acute Sleep Deprivation Increases Serum Levels of Neuron-Specific Enolase (NSE) and S100 Calcium Binding Protein B (S-100B) in Healthy Young Men*, Sleep 2014; 31(1): 19-198.
[39] Motomura Y. et al., *Sleep Debt Elicits Negative Emotional Reaction through Diminished Amygdala-Anterior Cingulate Functional Connectivity*, PloS ONE (2013); 8(2), e56578l; Fjell A.M. et al., *Self-Reported Sleep Relates to Hippocampal Atrophy across the Adult Lifespan: Results from the Lifebrain Consortium*, Sleep 2020; 45(3): 1-15.
[40] Taki Y. et al., *Sleep Duration during Weekdays Affects Hippocampal Gray Matter Volume in Healthy Children*, 60 NeuroImage 2012; 60(1):471-475.
[41] *Id*.; Noh, H.J. et al., *The Relationship between Hippocampal Volume and Cognition in Patients with Chronic Primary Insomnia*, J. Clinical Neurology 2012; 8(2): 130-138; Joo E.Y et al., *Hippocampal Substructural Vulnerability to Sleep Disturbance and Cognitive Impairment in Patients with Chronic Primary Insomnia: Magnetic Resonance Imaging Morphometry*, Sleep 2014; 37(7): 1189-1198.

of waste metabolites from the brain.[42] Sleep typically clears the brain of toxins and plaques which accelerate cognitive decline; disturbed sleep increases these dangerous concentrations. Accordingly, there is a bidirectional relationship between sleep and Alzheimer's disease. Sleep loss increases the cerebrospinal fluid concentration of insoluble brain plaques (amyloid-β and tau) which are associated with neuronal loss, synaptic loss, and cognitive dysfunction in Alzheimer's Disease by nearly 30%.[43] Chronic sleep deprivation accelerates the spread of tau protein aggregations throughout the brain.[44] After extended sleep loss, the brain's immune system turns against itself: "portions of synapses are literally eaten by astrocytes because of sleep loss."[45] Chronic sleep loss can lead to permanent cell damage and neuronal death.[46]

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[42] Hauglund N.L. et al., *Cleaning the Sleeping Brain – the Potential Restorative Function of the Glymphatic System*, Current Opinion Physiology 2020; 15: 1-6.
[43] Barthélemy N.R., et al., *Sleep Deprivation Affects Tau Phosphorylation in Human Cerebrospinal Fluid*, 87 Annals Neurology 2000; 87(5): 700-709.
[44] Holth, J.K.et al., *The Sleep-Wake Cycle Regulates Brain Interstitial Fluid Tau in Mice and CSF Tau in Humans*, Science 2019;363(6429):880-884.; Wang C. & Holtzman, D.M., *Bidirectional Relationship between Sleep and Alzheimer's Disease: Role of Amyloid, Tau, and Other Factors*, Neuropsychopharmacology 2020; 45(1):104-120.
[45] Coghlan, A. *The brain starts to eat itself after chronic sleep deprivation*, NewScience (May 23, 2017), https://www.newscientist.com/article/2132258-the-brainstarts-to-eat-itself-after-chronic-sleep-deprivation/#ixzz6qFwUWJXK.
[46] Jan J.A. et al., *Long-term sleep disturbances in children: A cause of neuronal loss*, Euro. J. Paediatric Neurology 2010; 14(5): 380-390.

Structural changes in the brain are linked to functional changes, and in turn related to changes in behavior. Sleep loss can beget functional changes including a significant decrease in the functional connectivity between the amygdala and the ventral anterior cingulate cortex (vACC), and hyperactivity of the left amygdala, in proportion to the degree of sleep debt. This decrease is significantly correlated with deterioration of subjective mood state. Sleep quality can significantly predict changes in depression and PTSD symptoms, supporting the causal role of insomnia in the development of psychological issues.[47]

Sleep loss not only damages the brain, but impairs the brain's repair systems. Sleep disruptions, as well as chronic stress, are both associated with impaired secretion of trophic factors, including brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1). These trophic factors modulate learning, memory processes, neuronal plasticity, and tissue repair.

C. Aggravating Substance Use Disorder

The plaintiff has argued that his confinement in solitary was the result of a substance use disorder (SUD). There is a demonstrable link between the conditions endemic to solitary confinement and the exacerbation of SUD symptoms. Substance use disorder is a chronic, recurrent mental disorder characterized by

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[47] Wright K.M. et al., *Insomnia as Predictor versus Outcome of PTSD and Depression among Iraq Combat Veterans*, J. Clinical Psychol. 2011; 67(12):1240-1258.

strong cravings, high recurrence rates, and a high proportion of comorbidity of mental and physical disorders. Importantly, SUD is recognized across the psychiatric field as a mental illness, and is included in the DSM 5, the standard classification of mental disorders used by mental health professionals in the United States. Further, SUD is treatable mental disorder. Indeed, medication assisted treatment is associated with substantial reductions in both risk and relapse in people with SUD. Absence or cessation of treatment, whether caused by health providers withholding such treatment or by personal choice of drug users, greatly increases likelihood of death.[48]

i. Social Isolation and Substance Use Disorder

Multiple studies have suggested a primary driver of drug addiction, in addition to neurochemical vulnerability, is the isolation, pain, and distress experienced by users.[49] Positive social interactions have several effects that are hypothesized to ameliorate addiction. They can provide many of the healthy, non-

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[48] Sordo, L. et al., *Mortality Risk during and after Opioid Substitution Treatment: Systematic Review and Meta-Analysis of Cohort Studies*, BMJ 2017; 357: j1550.
[49] Hari, J. *Chasing the Scream: The First and Last Days of the War on Drugs*, Bloomsbury Publ'g USA (2015).

drug reinforcers that successfully compete with drug rewards and that might also protect against the negative consequences of social stressors. [50]

Social isolation has the opposite effect. It has been shown to exacerbate pre-existing anxiety and depression, which are both highly comorbid with harmful substance use in emerging adulthood. Indeed, social isolation during treatment for addiction significantly predicts likelihood of relapse, future incarceration, and commission of a violent crime in the 12-months post-treatment.[51] Incredibly, participants reporting feeling estranged from others more than double their odds of future relapse and incarceration.[52]

Models in which laboratory animals self-administer drugs are widely regarded as valid because rodents and monkeys learn to self-administer most drugs abused by humans.[53] In primate models, studies of intravenous drug self-administration suggest individual differences in susceptibility to cocaine abuse within a population are profoundly influenced by environmental factors, in

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[50] Rynes, K. N., & Tonigan, J. S., *Do social networks explain 12-step sponsorship effects? A prospective lagged mediation analysis*, 26 Psychology of Addictive Behav. 2012; 26(3): 432-439.

[51] Johnson B.R. et al, *Alone on the Inside: The Impact of Social Isolation and Helping Others on AOD Use and Criminal Acitivity*, Youth Soc. 2018; 50(4) 529-550.

[52] Johnson B.R. et al, *Alone on the Inside: The Impact of Social Isolation and Helping Others on AOD Use and Criminal Acitivity*, Youth Soc. 2018; 50(4) 529-550.

[53] Panlilio LV& Goldberg S.R., *Self-Administration of Drugs in Animals and Humans as a model and an investigative tool*, Addiction 2007; 102(12) 1863-1870.

particular the social setting of housing conditions.[54] In rats, memories of amphetamine-and ethanol-paired contextual stimuli are acquired faster in socially isolated rats and, once acquired, amphetamine-associated memory is more resistant to extinction. [55] Socially isolated rats show greater propensity to self-administer amphetamine and cocaine relative to rats housed in enriched environments.[56]

Brain imaging data in humans suggests that levels of dopamine receptors that predict the subjective effects of stimulants, with implications for potential drug abuse, also depend in part on environmental factors including social isolation.[57] Experimentally induced social exclusion activates a brain network that overlaps with the pain matrix, which includes the insula.[58] Activity in the insula also correlates with the intensity of subjective craving for most addictive drugs in

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[54] Morgan D et al, *Social Dominance in Monkeys: Dopamine D2 Receptors and Cocaine Self-Administration*. *Nature Neuroscience 2002;* 5 (2): 169–74.
[55] Whitaker, LR, et al, *Social Deprivation Enhances VTA Synaptic Plasticity and Drug-Induced Contexual Learning*, Neuron 2013; 77(2): 335-345.
[56] Klebaur, J. E., et al. *Individual Differences in Behavioral Responses to Novelty and Amphetamine Self-Administration in Male and Female Rats*. Behavioural Pharmacology 2001; 12 (4): 267.
[57] Volkow, N. D. et al. *Prediction of Reinforcing Responses to Psychostimulants in Humans by Brain Dopamine D2 Receptor Levels*. The American Journal of Psychiatry 1999; 156 (9): 1440–43.
[58] Eisenberger, N.I. et al. *The Pain of Social Disconnection: Examining the Shared Neural Underpinnings of Physical and Social Pain*. Nature Reviews: Neuroscience 2012; 13 (6): 421–34.; Wager, T. et al, *An fMRI-Based Neurologic Signature of Physical Pain*. The New England Journal of Medicine 2013; 368 (15): 1388–97.

humans, suggesting that this region may be involved in both social exclusion and drug addiction.[59]

The insula is a brain area known to support subjective feeling states and cognition. The insula processes visual and interoceptive cues (the body's internal cues) to generate subjective feeling states and is thought to assign importance to stimuli associated with those states. In essence, it links salient information with subjective feeling states. This interplay is thought to have a large role in motivation, or the conscious drive to engage in behaviors. Dysfunction of the insula leads to motivational deficits, including those in substance use disorders. Drug induced cues can influence motivational salience and affect decision making behaviors. Recent meta-analyses have shown that drug-associated cues can recruit insular activity in substance using individuals. [60]

Neuroimaging studies, brain stimulation studies, and lesion (injury) studies all support this link between abnormal insula activity, social isolation and exacerbation of substance use disorders. A mechanistic role of insula activation in drug craving is supported by findings that insula lesions caused by stroke and

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[59] Garavan, H. *Insula and Drug Cravings*. Brain Structure & Function 2010; 214 (5-6): 593–601.
[60] Kühn S, Gallinat J. *Common biology of craving across legal and illegal drugs - a quantitative meta-analysis of cue-reactivity brain response.* Eur J Neurosci. 2011;33:1318–1326.; Engelmann JM, et al. *Neural substrates of smoking cue reactivity: A meta-analysis of fMRI studies*. Neuroimage. 2012;60:252–262

insula-targeted transcranial magnetic stimulation both reduce cigarette craving and smoking.[61] Further, low insula activity in a risk task predicts increased risk of relapse in abstinent methamphetamine users.[62] A recent positron emission tomography study showed that social acceptance is associated with activation of natural, endogenous opioids in the anterior insula and the amygdala, while social isolation is linked to deactivation of these systems. In addition, there is increasing support for the overlap of neural circuitry supporting physical pain and "social pain," which are both modulated by endogenous opioids.[63] A key role for endogenous opioids in the link between addiction and social pain has recently been proposed suggesting that social integration, by restoring normal function of endogenous opioid systems, can decrease the need to activate these systems through alcohol or opioid use and subsequently can decrease drug use and

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[61] Naqvi et al., *Damage to the Insula Disrupts Addiction to Cigarette Smoking*, Science 2007; 315(5811):531-534; Dinur-Klein, L. et al., *Smoking Cessation Induced by Deep Repetitive Transcranial Magnetic Stimulation of the Prefrontal and Insular Cortices: A Prospective, Randomized Controlled Trial*, Biological Psychiatry 2014; 76(9): 742-749.

[62] Gowing J.L. et al., *Attenuated Insular Processing during Risk Predicts Relapse in Early Abstinent Methamphetamine-Dependent Individuals*, Neuropsychopharmacology2014; 39(6): 1379-1387.

[63] Eisenberger NI. *The pain of social disconnection: examining the shared neural underpinnings of physical and social pain*. Nat Rev Neurosci. 2012;13:421–434

relapse.[64] These data indicate social isolation is a key risk factor in substance use and relapse, and that segregation is a particularly damaging housing environment for individuals with SUD.

ii. Stress and Addiction

There is substantial literature on the significant association between acute and chronic stress, both endemic to solitary confinement, and increased motivation to abuse addictive substances. Negative affect, including chronic stress, has been shown to statistically predict substance use.[65] With increasing levels of emotional and physiological stress or negative affect, there is a decrease in behavioral control and increases in impulsivity. With increasing levels of distress, and chronicity of stress, there is a greater risk of maladaptive behaviors including addictive behavior.[66] Addicted individuals show enhanced sensitivity to craving and greater anxiety in stress situations.[67] Neurobiological evidence shows that with increasing levels of stress, there is a decrease in prefrontal functioning and increased limbic-

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[64] Lutz P.E. & Kieffer, B.L. *The Multiple Facets of Opioid Receptor Function: Implications for Addiction*, Current Opinion in Neurobiology 2013; 23(4): 473-479.
[65] Costello J.E. et al., *Prevalence and Development of Psychiatric Disorders in Childhood and Adolescence*, 60 Archives of General Psychiatry 2003; 60(8) 837–844.; Mason A. W. et al., *Longitudinal Relations among Negative Affect, Substance Use, and Peer Deviance during the Transition from Middle to Late Adolescence*, Substance Use & Misuse 2009; 44(8) 1142 -1159.
[66] Sinha, R. *Chronic Stress, Drug Use, and Vulnerability to Addiction*, Annals N.Y. Acad. of Sci. 2008; 1141:105
[67] *Id*.

striatal level responding, which perpetuates low behavioral and cognitive control.[68] These motivational brain pathways are key targets of brain stress chemicals and provide an important potential mechanism by which stress affects addiction vulnerability by reducing behavioral control.

Prolonged and repeated stress adversely affects development of the prefrontal cortex (PFC), a brain region that is highly dependent on environmental experiences for maturation. The PFC, and particularly the right PFC, plays an important role both in activating the autonomic responses to stress and in regulating stress responses and cognitive control.[69] Social defeat stress also alters feedback from the PFC and has been shown to increase drug self-administration.[70] Human studies on the neurobiological effects of child maltreatment document neuroendocrine changes as well as alterations in size and volume of prefrontal, thalamic, and cerebellar regions associated with maltreatment and with initiation of

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[68] Li, C-L, & Sinha,R, *Inhibitory Control and Emotional Stress Regulation: Neuroimaging Evidence for Frontal-Limbic Dysfunction in Psycho-Stimulant Addiction*, 32 Neuroscience and Biobehavioral Reviews 2008; 32(3): 581-597.
[69] Gratton A. & Sullivan, R.M., 2005. "Chapter 6.3 - Role of Prefrontal Cortex in Stress Responsivity." In *Techniques in the Behavioral and Neural Sciences*, edited by T. Steckler, N. H. Kalin, and J. M. H. M. Reul, 15:807–17. Elsevier.
[70] Miczek, K. A. et al., *Aggression and Defeat: Persistent Effects on Cocaine Self-Administration and Gene Expression in Peptidergic and Aminergic Mesocorticolimbic Circuits*, 27 Neuroscience and Biobehavioral Reviews 787 (2004).

addiction.[71] Together, the data presented highlight the significance of stress effects on prefrontal regions involved in behavioral control in the context of addiction, and suggest that stressful environments have potential to exacerbate Substance Use Disorder.

iii. Sleep Deprivation, Impulsivity, Cognitive Control, and Substance Abuse

Disruption of sleep, endemic to solitary confinement, facilitates drug-taking behaviors in humans. [72] Neuroimaging studies have confirmed the interplay between reward and reinforcement pathways (ventral striatum/nucleus accumbens and orbitofrontal, dorsal, and lateral regions of the prefrontal cortex) and inhibitory pathways (amygdala, insula, anterior cingulate, right inferior frontal gyrus, subthalamic nucleus, and supplementary motor areas of the prefrontal cortex) associated with impulsivity and drug abuse vulnerability.[73] Sleep deprivation specifically impairs addiction treatment by increasing impulsivity and reducing

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[71] De Bellis, D.M. *Developmental Traumatology: A Contributory Mechanism for Alcohol and Substance Use Disorders*, Psychoneuroendocrinology 2002; 27(1-2):155-1170; De Bellis. D.M. et al., *Prefrontal Cortex, Thalamus, and Cerebellar Volumes in Adolescents and Young Adults with Adolescent-Onset Alcohol Use Disorders and Comorbid Mental Disorders*, Alcoholism, Clinical and Experimental Research 2005; 29(9): 1590-1600.

[72] Puhl, MD et al., *A Novel Model of Chronic Sleep Restriction Reveals an Increase in the Perceived Incentive Reward Value of Cocaine in High Drug-Taking Rats*, Pharmacology 2013; 109 :8-15.

[73] Moningka H, et al., *Current Understanding of the Neurobiology of Opioid Use Disorder : An Overview*. Curr. Behav. Neurosci Rep. 2019 ; 6(1) :1-11.

cognitive control, both reversing treatment success and precipitating relapse to drug use.[74]

Clinical studies have suggested that low sleep quality is a factor that significantly predicts relapse in addicts.[75] The nucleus accumbens, an area in the brain involved with the anticipation of reward and impulsivity in drug use, becomes selectively more active under conditions of sleep deprivation.[76] Impulsivity is predominant among users of several drugs of abuse including alcohol, cocaine, and amphetamines. It is considered a risk factor for later development of alcohol and substance abuse and dependence, and is of the key predictors of drug use and relapse is impulsivity.[77] In addition, sleep loss further potentiates the dopaminergic neurotransmission in the nucleus accumbens. Both drug-induced reinforcement and drug-environment conditioning seem to be related to increased responsiveness of the dopaminergic system.[78] Cognitive control

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[74] Berro, LF et al, *Relationships between Sleep and Addiction: The Role of Drug-Environment Conditioning*, Medical Hypotheses 2014; 82(3): 374-376.
[75] Brower, K.J., *Alcohol's Effect on Sleep in Alcoholics, Alcohol Research and Health*, The Journal of the National Institute on Drug and Alcohol Abuse and Alcoholism, 2001 ; 25(2) : 110-125.
[76] Venkatraman V et al, *Sleep Deprivation Elevates Expectation of Gains and Attenuates Response to Losses Follwing Risky Decisions*. Sleep 2007 ; 30(5) 603-609.
[77] Dalley J.W. et al, *Impulsivity, compulsivity and top down cognitive control*. Neuron 2011 ; 69(4) : 680-694.
[78] Volkow, N.D, et al, *The Neuroscience of Drug Reward and Addiction*, Physiol Rev. 2019 ; 99 : 2115-2140.

abilities are tightly related to central dopaminergic activity, which is altered by sleep deprivation, and sleep deprivation impairs cognitive control increasing likelihood of failures of behavioral control such as relapse.[79] Thus, sleep deprivation and the subsequent hyperactivity and dopaminergic shifts in the nucleus accumbens could likely facilitate drug taking behaviors.

II. SOLITARY CONFINMENT INFLICTS LONG LASTING PSYCHOLOGICAL HARM UPON PRISONERS

Solitary confinement such as the confinement plaintiff has alleged imposes conditions which deprive prisoners of the social interaction, environmental stimulation and the tools of self-regulation required for basic cognitive and emotional functioning. This complete social isolation causes unique injury over and above that of typical carceral settings. The solitary confinement scientific literature describes a wide range of symptoms, which include anger, stress, the loss of reality testing, suicidality, insomnia, poor concentration, confusion, depression and hallucinations.[80] Many studies demonstrate that serious symptoms can occur in

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[79] Mantua J & Simonelli G*, Sleep Duration and Cognition: is there an ideal amount?*, Sleep 2019; 42(3): 1-3.
[80] Haney, C, *The Psychological Effects of Solitary Confinement: A Systematic Critique*, 2018; Crime & Just, 47 (1): 365-416, Scharff Smith, P., *The Effects of Solitary Confinement on Prison Inmates: A Brief History and Review of the Literature*, 2006; 34 Crime and Justice, 441-528.

healthy individuals within days to weeks in isolation and the amount of time spent in isolation increases its damaging effects.[81]

A. Psychological and Behavioral Effects of Solitary Confinement

The mental and behavioral correlates of the neurologic injuries inherent in extreme segregation are myriad. Prisoners commonly experience cognitive dysfunction, severe depression, anxiety and panic, delusions and hallucinations as well as perceptual disturbances.[82] Inmates often display poor impulse control and spontaneous outbursts of violence, as well as profound social withdrawal. As discussed above, the memory deficits, anxiety and poor affect regulation would be expected with involvement of the hippocampus, the amygdala and the pre-frontal cortex – areas known to subserve memory, emotion regulation and executive functioning.[83]

Empirical studies have identified adverse psychological reactions to the sleep disruption endemic to solitary confinement, particularly with continuous illumination and loud noises. When combined with chronic stress, sleep disturbance is linked with decreased appetite, tachycardia, persistent fear and a

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[81] Volkart, R, et al, *Solitary confinement as a risk factor for psychiatric hospitalization*. Psychiatric Clin (Basel) 1983,16 (5-6) 365-377.
[82] Grassian, S, *The Psychiatric Effects of Solitary Confinement*. 22 Wash U. J.L. & Policy 325- 383 (2006).
[83] McEwen et al, *Stress Effects on Neuronal Structure: Hippocampus, Amygdala and Prefrontal Cortex*, 41 Neuropsychopharmacology 2016; 41: 3-23.

sense of impending emotional breakdown. Sleep disturbance is also associated with panic, anxiety, aggression and rage.[84] As with Mr. Cintron, self-injurious behavior is also frequent in these settings, including mutilation or amputation of body parts as well as self-inflicted wounds and fractures.[85] Prisoners in solitary confinement have rates of suicide and self-mutilation that are estimated to be almost 7 times greater than that of prisoners in the general population.[86] These psychological and behavioral effects are more severe in prisoners with preexisting mental illnesses who are placed in solitary confinement. However preexisting mental illness does not account for the deleterious effects that go beyond those of general incarceration.[87]

B. Impacts Continue Even After Release from Extreme Segregation

The psychological harms caused by solitary confinement can persist after cessation of isolation and interfere with post-incarceration rehabilitation. The persistent impairments include heightened anxiety, agoraphobia and panic disorder, as well as impairments in interpersonal communication. Detainees exhibit

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[84] Haney, C, *The Psychological Effects of Solitary Confinement: A Systematic Review*, Crime & Just. 2018; 47(1): 365-416 (2018).
[85] Grassian S, *Psychopathological Effects of Solitary Confinement*, Am. J Psychiatry 1983, 140(11) 1450 -1454.
[86] Kaba, F, et al. *Solitary Confinement and the Risk of Self-Harm Among Jail Inmates*, Am. J. Pub. Health 2014; 104(3), 442-447.
[87] Luigi M, et al, *Shedding Light on "the Hole": A Systematic Review and Meta-Analysis on Adverse Psychological Effects and Mortality following Solitary Confinement in Correctional Settings*, Front: Psychiatry 2020; 11 (2020)

difficulties with social interactions and a tendency towards social withdrawal as well as a generalized antipathy for human interactions.[88] While some detainees experience a gradual amelioration of symptoms, others are socially disabled and continue to experience the negative health effects of their extreme segregation.[89]

Leading researchers in the field have concluded that the longer the time spent in isolation, the greater the likelihood that the impairments will be permanent.[90] Several studies report the persistence of confusion, impaired memory, poor concentration and sleep disturbance.[91] Others note the prevalence of impairments in interpersonal and familial relationships after release.[92] The persistent negative effects also impact survival rates. A recent study demonstrated that any amount of time in solitary confinement increases the risk of death in the first year after return to the community. This large cohort study demonstrated that those who spent time in solitary confinement were 24% more likely to die in the

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[88] Shen, F, Neuroscience, *Artificial Intelligence and the Case Against Solitary Confinement, Vanderbilt Journal of Entertainment and Technology Law*, 2020; 21, 937 -1017. Reiter et al, *Psychological Distress in Solitary Confinement: Symptoms, Severity and Prevalence in the United States, 2017-2018*. American Journal of Public Health 2020 110: S56-S62.
[89] Scharff Smith, P., *The Effects of Solitary Confinement on Prison Inmates: A Brief History and Review of the Literature,* 2006; 34 Crime and Justice, 441-528.
[90] Haney, C, *Mental Health Issues In Long-Term Solitary and "Supermax" Confinement*, Crime and Delinquency 2003; 49(1): 124-156.
[91] Salev, S. *A Sourcebook on Solitary Confinement*, ssrn-id21277495, 2008.
[92] Grassian S, *The Psychiatric Effects of Solitary Confinement*, Journal of Law and Policy, 2006; (22) 325-383.

first year after release, particularly from suicide (78% more likely) and homicide (54% more likely) and were 127% more likely to die from an opioid overdose in the first two weeks of release.[93]

[93] Brinkley-Rubenstein, L, Sivaraman, J, Rosen DL, *Association of Restrictive Housing During Incarceration with Mortality After Release*. JAMA 2(10) (2019).

CONCLUSION

Neuroscientific research establishes that prolonged solitary confinement presents the substantial risk of significant harm to the brain. This Court should affirm the district court's order on the Defendants-Appellants' motion for judgment on the pleadings and return the matter to the district court for further proceedings on the merits of Plaintiff-Appellee's claims for relief.

Dated: May 11, 2023

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CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limitation of Fed. R. App. P. 32(a)(7)(B) because, excluding parts of the brief exempted by Fed. R. App. P. 32(f), this document contains 9,160 words.

This brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6) because this document has been prepared in a proportionally spaced typeface using Microsoft Word with Times New Roman in 14-point type.

Dated: May 11, 2023

/s/ Nancy Gertner
Nancy Gertner

CERTIFICATE OF SERVICE

I certify that on May 11, 2023, the foregoing Amici Curiae Brief was filed electronically through the Court's CM/ECF system. Notice of this filing will be sent by email to all parties by operation of the Court's electronic filing system.

Dated: May 11, 2023

/s/ Nancy Gertner
Nancy Gertner