**Serotonin 5-HT2A Receptor Activation in Near Death Experiences**

Serotonin (5-HT) and its low-affinity 5-HT2A receptors1-8 are highly conserved evolutionarily2,4 and implicated in nearly all pscyho-biological processes of cells, systems, and organisms, including sensation and perception;9 emotion;9,10 sleep, wakefulness, and alertness;4,11,12 stress responses;13-18 cell survival;11,12,15,19-24 persistence and resilience;11,13,17,25-29 cell death processes;11,19,20,22,23,30-40 **near-death processes** (including asphyxiation/hypoxia12,39,40 **and cardiac arrest39,40**); and altered states of consciousness (including schizophrenia,4,10,41,42 psychedelic use,43-51 hallucinations,10,47 transcendental meditation,52 spirituality,53 and **near death experiences39,40**)(e.g., [Moutkine et al., 2018](https://pdf.sciencedirectassets.com/272488/1-s2.0-S1043661818X00139/1-s2.0-S1043661818313252/am.pdf?X-Amz-Security-Token=IQoJb3JpZ2luX2VjEHAaCXVzLWVhc3QtMSJGMEQCIFeRtwORJq1GBQ19lv%2FhwApcDvqgXjW0%2Bp%2FW8Cm6Lv2eAiBxhRsI2dLOlPS9WU21A5ELI0875YJ5955YvyPl41Mz0CqzBQgYEAUaDDA1OTAwMzU0Njg2NSIMpqwa9I6kpxVIbxReKpAFI0y%2BJ6GCZ1fs8UE8BcBoTirbV2Dreyyt7X9VzNUf6FcQDw%2FNl1uh9X%2FO%2FEDDSz3YfH1q%2FK93VJfixzKM%2FnsQqAYwgKfFSk1Hbsha1eS1rwZ%2F8PWcxInqOGntYK1Zv7dwHh0Ee0aUL%2F2DzMs19CxALReqrtscgbyZgLiNoHAXwIe6X25%2BMdPEdv7ZqRe3xhdJKI82J9O1g75buFbIuDSRs%2FwD2dw2yzVpDjPnjCT5ohKm6wDXQyOE4Q6%2BYYuca8sAb93rxbFwvL1ez6tL%2FvuuGPac7%2BOywu7d%2FX07%2BxM36%2FtZC44uFKFNn7DHmjueB3UzGJpM1n4slOm5EC4vJ6tS4COe%2FEz3cXfBY9ZCtWqdhvP9QZRoQTlpC5rxlwrfmpm7M2pBtbd0gUTdsvG%2F57XmFvqTrtL8l5DS0pipMOLiXILCJSe09vVqA4FLkUo2g0WBbGQFxn2u2Q%2BzCXj9TDLNxdaU7OVNnyWys5OnEGFcSvu%2F3s1BNFD3FZmvRnoHuGlhNKF6liJBWYWSupm79OCo6JILI%2FvtJMuxERitNmadLOQIShHBwmUZ70CQp8cLtBqDmyOsurtWVnlIV5K%2B3f0rtd%2Fj4CoXTMXfPDSS8wXWHWgJUv76vhFZvZ0lMmCS63ECi7oudhdXoHWKykmyiajiyhekymijZBDEZa3%2FmYM2weBb723BOMAQm6zJQvAOGwVqmVkeTuOyrHGCX4H%2Ba3k2UF4%2FfCGSOapv4%2FbDjCF0TmfF76dM1pHoCrA6lrdxY9xDR8CIRcjMdk%2FvQK3Tz0hgw2e0LInOBegHqne0EbVX0kVLnQuw3bMNIm7XImoItlshcY0kyDIX8SMo4s52Rwd84juh3oPoLu69eT1JYa%2BmpuIw3quSugY6sgF8vTw65%2BrfD1JXUC2EdqhMSJ09gdx8WkzyjD6rAu%2Bs8H%2B5GaTiI7UhUnfqtvBOFHqRhuNk38bbPXXXgD8TjQPL3O%2Fuynzb3Z%2BYG6dLHN%2FMAwAAPlCCEGdQ3lI25uvjEcMi3kU7EqXsElFhO5AE7lfA86sNQpT0F5nCrPVA5lS9r8wXeOKBzoKFEMZ%2FTjycu9VRk23CRqujd9gokk8MTOeDFCpg82dvB03EJvAeFiKRMmAr&X-Amz-Algorithm=AWS4-HMAC-SHA256&X-Amz-Date=20241125T161359Z&X-Amz-SignedHeaders=host&X-Amz-Expires=300&X-Amz-Credential=ASIAQ3PHCVTY4XGXGQIX%2F20241125%2Fus-east-1%2Fs3%2Faws4_request&X-Amz-Signature=ce7adb6afa56e7806ca9f118c81566b9fe4ab64829a53e5a29f572abb924be13&hash=486a92783c4b22d3a4b023ee6f14cd75bd45e78033c285646d060f8e3c8bee1a&host=68042c943591013ac2b2430a89b270f6af2c76d8dfd086a07176afe7c76c2c61&pii=S1043661818313252&tid=pdf-7cf4e307-75e6-4d31-a178-d0fa3d59a3ca&sid=87e9cfa4869ee841973b83025dadc0e828c7gxrqa&type=client); [Roth et al., 1998](https://pubmed.ncbi.nlm.nih.gov/10348614/); [Bray et al., 2004](https://pubmed.ncbi.nlm.nih.gov/14699448/); [Bray 2018](https://search-proquest-com.ezproxy.usd.edu/docview/2157998281?accountid=14750); [Nichols & Nichols 2019](https://orbi.uliege.be/bitstream/2268/291053/1/alius_bulletin_n°4.pdf#page=24)). The 5-HT-2A receptor’s low binding affinity for serotonin (~1.3 nM Ki/KD)37,43,54 requires high concentrations of extracellular serotonin to be present for receptor activation.1,9,11,37,55,56 This implicates 5-HT2A receptor activation in conditions of high stress, intense emotional or psychological states, serotonergic pharmacotherapy use (e.g., SSRIs, SNRIs, and serotonergic psychedelics), **and near-death experiences** that increase extracellular serotonin levels sufficient for 5-HT2A receptor activation ([Li et al., 2015](https://pmc.ncbi.nlm.nih.gov/articles/PMC4413312/pdf/pnas.201423936.pdf); [Nichols & Nichols 2019](https://orbi.uliege.be/bitstream/2268/291053/1/alius_bulletin_n°4.pdf#page=24)).10,39,40 A variety of in vitro and in vivo studies demonstrate that cardiac arrest, hypoxia, and asphyxiation are associated with robust increases in extracellular neurotransmitter concentrations (including serotonin) in the cortex, limbic brain regions, and other areas of the brain (e.g., [Li et al., 2015](https://pmc.ncbi.nlm.nih.gov/articles/PMC4413312/pdf/pnas.201423936.pdf); [Nichols & Nichols 2019](https://orbi.uliege.be/bitstream/2268/291053/1/alius_bulletin_n°4.pdf#page=24); [Bray, 2018](https://search-proquest-com.ezproxy.usd.edu/docview/2157998281?accountid=14750)).39,40,57,58 For example, [Li et al., 2015](https://pmc.ncbi.nlm.nih.gov/articles/PMC4413312/pdf/pnas.201423936.pdf) found that in adult rats undergoing experimental asphyxiation, serotonin levels increased in the frontal and occipital lobes from ~0nM to ~13 nM and ~18 nM at 1 and 2 min post asphyxia respectively (~ 13x and 22x above baseline (BL) levels and associated with >80% of 5-HT2A binding occupancy in the rat cortex43,54).58 Serotonin levels peaked at ~63 nM at 5 min in the frontal lobe and ~42 nM at 4 and 8 min in the occipital lobe (~70x and 245x > BL respectively, associated with >~90–97% receptor occupancy43,54), before gradually decreasing to ~33 nM and ~18nM at 20 min post asphyxiation, when recordings were ended (~150x and ~70x > BL and associated with >80% binding occupancy43,54).58 Similar increases have been observed by others in limbic brain regions (e.g., in the nucleus accumbens by Bray, 2018 and Bray et al., 2020)57,59 and are braodly considered adequately sufficient to activate and saturate 5-HT2A receptors39,40,54,57,58 *and* induce the “visual hallucinations and mystical feelings” associated with near death experiences in humans.10,47,53,58,60,61 Notably, Li et al (2015) also observed rapid increases in extracellular levels of glucose, adenosine, dopamine, norepinephrine, GABA, glutamate, and aspartate in the frontal and occipital lobes at levels sufficient to achieve receptor saturation.58 These findings are mirrored by Bray et al’s observations of increases in dopamine, norepinephrine, and ascorbic acid in the nucleus accumbens (core and shell).57,59 Li et al (2015) note that the “immediate surge of cortical release of … critical neurotransmitters” is associated with “a robust and sustained surge of functional and effective cortical connectivity” as assessed by EEG, suggesting functional receptor binding.58 The observed increases in dopamine also implicate activation of the Dopamine D2R receptor as possibly implicit in the hallucinations often associated with near-death experiences.60

[Psychological States: Intense emotional or psychological states can also elevate serotonin levels2](https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2015.00225/full).

5-HT2A receptor is associated preceptions of connectivity, activity, desensitization, and suicide reversal at the level of the cell, system, and organism biologically and psychologically,5,7,9,62 as well as psychological states of non-ordinary consciousness that can include feelings of connectedness, peacefulness, spirituality, euphoria, 'hallucinations,' and disassociation from life in this realm ([Borg et al., 2003](https://psychiatryonline.org/doi/epdf/10.1176/appi.ajp.160.11.1965); [Wallach et al., 2023](https://pubmed.ncbi.nlm.nih.gov/38102107/); [Kwan et al., 2022](https://pubmed.ncbi.nlm.nih.gov/36280799/); [Holze et al., 2024](https://www.sciencedirect.com/science/article/pii/S245190222400020X); [Bujatti et al., 1976](https://www.bujatti.at/wp-content/uploads/Seratonin1976.pdf); [Buchanan et al., 2015](https://journals.physiology.org/doi/epdf/10.1152/jn.00213.2015); [Bray et al., 2004](https://pubmed.ncbi.nlm.nih.gov/14699448/)). 4,9,11,43,48,52,53,61-65

Paragraph on when 5-HT2A is activated (near death and non-ordinary states of consciousness like psychedelics, meditation, and hypnosis).

Paragraph on near death exerperiences in cardiothoracic surgery

It may be that these incidences causes release of cellular serotonin in the extracellular space sufficient to activate 5-HT2A receptors, thus producing the euphoric effects reported in near-death experiences and characteristic of 5-HT2A activation.

In this cross-sectional mixed methods study, we will explore themes across cases of near death experience that occur during cardiothoracic surgery and test mechanisms that can explore 5-HT2A receptor binding during these processes.

**In aim 1,** we will conduct a cross-sectional, mixed-methods study to explore psychological experiences associated with near death during cardiothoracic surgery (NDDCS). Up to 30 patients who experience NDDCS will be invited to participate in one-to-two-hour semi-structured anonymously recorded zoom interviews with Dr. Bray. Interview questions will inquire about biological, psychological, and spiritual sensations, perceptions, beliefs, and other experiences associated with NDDCS as well as short- and long-term experiential changes. Some questions will also specifically inquire about similarities and differences of their sensations, perceptions, and experiences as compared to those associated with 5-HT2A receptor activation, psychedelic drug use, and other states of non-ordinary consciousness. Interview recordings will be transcribed and transcripts will be qualitatively analyzed for themes using reflexive thematic analysis (Bray et al., 2022, 2023a,b, 2024). Participant views that support, negate, or are not associated with each theme will be qualified and expressed as number and percent of the total sample.

**In aim 2**, up to five consenting individuals who experience NDDCS will undergo 5-HT2A-tagged PET scanning immediately after defibrillation. Findings will be compared with those of up to five consenting individuals who undergo comparable cardiothoracic surgeries without near death experiences. Participants will be matched for mental health diagnoses, specifically including depression, suicidality, and prescription medication and psychedelic and psychotropic use. Though under-powered, T-tests and ANOVAs will be used to assess whether 5-HT2A receptor activation differs between these two groups (NDDCS vs. control). Findings from this pilot study will be used to generate pilot data for a larger grant application. Additionally, 5-HT2 receptor activation levels will be compared to qualitative NDDCS reports to assess whether any specific themes correlate with 5-HT2A receptor activation.

Findings from these studies will be presented at conferences locally, regionally, nationally, internationally, and virtually and published in peer-reviewed scientific manuscripts.

**Psychedelic drug use** (including synthetic (lab-made) and natural drugs/compounds like LSD and psilocybin mushrooms; see references above).

* + **Death and near-death experiences.**
    - When cells in brain die, they often “bleb” and release all of their contents - including all neurotransmitters - into their external environment, resulting in massive neurotransmitter dump into the extracellular space in the brain for brain receptor activation).
    - I don’t tend to see much research published on this in terms of possible relationships between death/near-death and activation of low affinity receptors like 5-HT2A that are not otherwise activated in normative endogenous states. However, I know from my graduate research that at a neurobiological level, death is preceded by extracellular serotonin dumping at amounts that are sufficient to activate 5-HT2A receptors (e.g., [Bray et al., 2020](https://pubmed.ncbi.nlm.nih.gov/31881169/); observed in this work by me but not reported in this publication).

1. The human brain and body are highly conservative ([Moutkine et al., 2018](https://pubmed.ncbi.nlm.nih.gov/30223085/)). Rarely do we see anatomy or functions that are conserved through time that do not have important functions or contributions to the human life experience ([Moutkine et al., 2018](https://pubmed.ncbi.nlm.nih.gov/30223085/)).
2. What, then, might be the biological function of 5-HT2A receptors in the brain? How might their use be harnessed in the context of life, death, pain, suffering, and healing/therapy/therapeutic modality?
3. **Death & Migration at the level(s) of the cell & the human**
4. The process(es) by which cells in the body die can be categorized into the one of several categories/processes (e.g., necrosis, autophagy, apoptosis).
   * [Yuan & Ofengeim, 2018. "A guide to cell death pathways."](https://pubmed.ncbi.nlm.nih.gov/38110635/)
   * [Newton, 2024, "Cell death."](https://pubmed.ncbi.nlm.nih.gov/38242081/)
   * [D'Arcy 2019. "Cell death: a review of the major forms of apoptosis, necrosis and autophagy."](https://pubmed.ncbi.nlm.nih.gov/30958602/)
   * [Bertheloot et al., 2021. "Necroptosis, pyroptosis and apoptosis: an intricate game of cell death."](https://pubmed.ncbi.nlm.nih.gov/33785842/)
5. One form of cell death (apoptosis) involves imitation of a "death" program. This is often referred to as "programmed cell death," akin to cellular suicide and it can occur in several different forms (see references above).
6. One form of apoptosis (programmed cell death) is called cellular "blebbing" (scientific term for "blistering") and it has an important role in facilitating the movement of cells from one location in the body to another (called "cellular migration").
   * [Charras 2008. “A short history of blebbing;"](https://pubmed.ncbi.nlm.nih.gov/18755002/)
   * [Fackler & Grosse, 2008. “Cell motility through plasma membrane blebbing;"](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2426937)
   * [Wickman et al., 2013. “Blebs produced by actin-myosin contraction during apoptosis release damage-associated molecular pattern proteins before secondary necrosis occurs;"](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3770329)
   * [Charras & Paluch, 2008. "Blebs lead the way: how to migrate without lamellipodia;"](https://pubmed.ncbi.nlm.nih.gov/18628785/)
   * [Paluch & Raz, 2013. “The role and regulation of blebs in cell migration"](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3989058).
   * [Charras et al., 2005. “Non-equilibration of hydrostatic pressure in blebbing cells"](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1564437)
7. If certain cell death processes can serve to facilitate cellular migration (migration of cells from one space to another) (Charras 2008, Fackler & Grosse, 2008; Wickman et al., 2013; Charras & Paluch, 2008; Paluch & Raz, 2013; Charras et al., 2005), **how might human death processes do the same thing?**
8. How might this question be explored through a scientific lens?
9. What aspects could be observed, measured, and studied?

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